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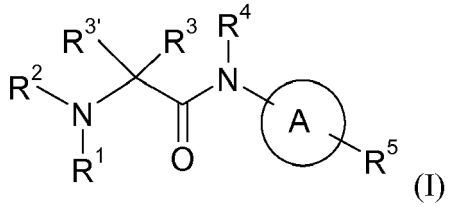
Remarks:
This application was filed on 11-12-2013 as a divisional application to the application mentioned under INID code 62.

(54) **Compounds which selectively modulate the CB2 receptor**

(57) Compounds of formula (I)



(I)

are disclosed. Compounds according to the invention bind to and are agonists, antagonists or inverse agonists of the CB2 receptor, and are useful for treating inflammation. Those compounds which are agonists are additionally useful for treating pain.

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Description

BACKGROUND OF THE INVENTION

1. TECHNICAL FIELD

[0001] The present invention relates to novel compounds which modulate the CB2 receptor and their use as medicaments.

2. BACKGROUND INFORMATION

[0002] WO2008014199, WO2008039645 discuss the CB2 receptor, and the therapeutic uses of the CB2 receptor agonist compounds disclosed therein. It is believed that the highly selective activation of the CB2 receptor with an agonist may offer avenues of harnessing the beneficial effects while avoiding the adverse effects seen with dual CB1/CB2 cannabinoid receptor agonists (see e.g. Expert Opinion on Investigational Drugs (2005), 14(6), 695-703). It is desirable therefore to provide agonists of CB2 with minimized CB1 activity.

[0003] PCT Application Number PCT/US09/34464 discloses compounds having CB2 agonist activity. The compounds of the present invention differ structurally from the above disclosed compounds, for example the present R5 in the formula (I) disclosed hereinbelow. Additionally, the compounds of the present invention have lower CB1 activity than the compounds disclosed in the cited art.

BRIEF SUMMARY OF THE INVENTION

[0004] The present invention provides novel compounds which bind to and modulate the CB2 receptor and have lower CB1 receptor activity. The invention also provides methods and pharmaceutical compositions for treating inflammation by way of the administration of therapeutic amounts of the compounds of the invention. Lastly, the invention provides a method and pharmaceutical compositions for treating pain by way of the administration of therapeutic amounts of the compounds of the invention.

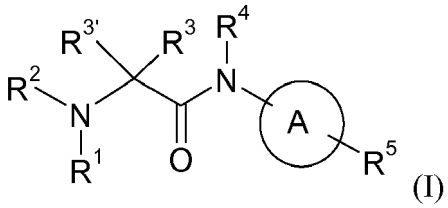
BRIEF DESCRIPTION OF THE FIGURES

[0005]

Fig. 1: Flow rate graph time vs %organic (B) using evaporative light scattering detectors.
Fig. 2: Flow rate graph time vs %organic (B) using HPLC-MS equipment.

DETAILED DESCRIPTION OF THE INVENTION

[0006] In the broadest generic embodiment 1, the invention provides compounds of the formula



(I)

wherein:

ring A is a 5-membered heteroaryl ring;

R^1 is hydrogen, C_{1-10} alkyl or C_{3-10} cycloalkyl which is optionally substituted with 1-3 C_{1-10} alkyl, each **R^1** or it's substituent is optionally halogenated;

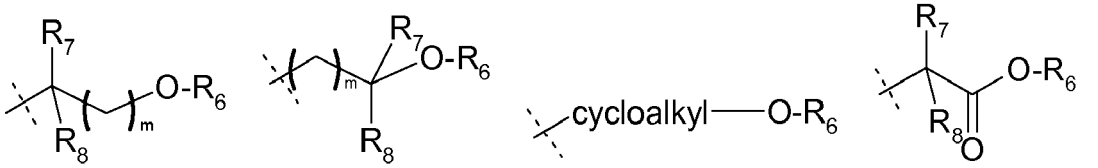
R^2 is C_{1-10} alkyl, C_{3-10} cycloalkyl, arylsulfonyl, arylcarbonyl, C_{1-10} acyl, C_{3-10} cycloalkylcarbonyl, heterocyclylcarbonyl, heteroarylcarbonyl, heterocyclyl, benzyl, phenethyl, aryl or heteroaryl each optionally independently substituted with 1 to 3 substituents chosen from C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6}

alkoxycarbonyl, C_{1-6} alkylamino, C_{3-6} cycloalkylamino, C_{1-6} dialkylamino, C_{1-6} alkylaminocarbonyl, C_{1-6} acylamino, C_{1-6} dialkylaminocarbonyl, hydroxyl, halogen, cyano, nitro, oxo, heterocyclyl, aryl and heteroaryl, each substituent on **R^2** where possible is optionally halogenated or substituted with 1 to 3 C_{1-6} alkyl, C_{1-6} acyl, C_{1-6} alkyl sulfonyl, cyano, aryl, oxo or hydroxyl; or **R^1** and **R^2** together with the nitrogen atom to which they are attached form a monocyclic, bicyclic or spirocyclic heterocycle or monocyclic or bicyclic heteroaryl ring each optionally substituted with 1 to 3 C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkyl sulfonyl, cyano, aryl, oxo, hydroxyl or halogen each ring substituent being further optionally halogenated where possible;

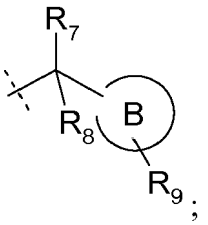
R^3 and **$R^{3'}$** are independently hydrogen or C_{1-6} alkyl optionally halogenated with the proviso that **R^3** and **$R^{3'}$** cannot simultaneously be hydrogen; or R^3 and $R^{3'}$ together with the carbon atom to which they are attached form a 3- to 6-membered cycloalkyl or heterocyclic ring each optionally halogenated;

R^4 is hydrogen or methyl;

R^5 is chosen from



and



m is 0,1, 2 or 3

R^6 is hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy

R^7 and **R^8** are each independently hydrogen, or C_{1-4} alkyl with the proviso that both R^7 and R^8 cannot be hydrogen; and wherein **R^7** and **R^8** optionally can cyclize to form a C_{3-7} cycloalkyl ring; **R^9** is C_{1-6} alkyl or aryl;

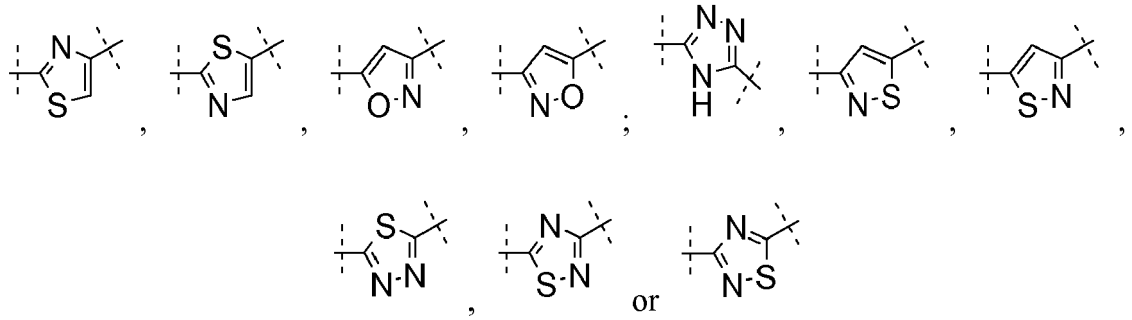
ring B is a 5-6 membered heterocyclic ring;

n is 0, 1 or 2;

wherein any carbon atom on the formula (I) or any R substituent listed above is optionally partially or fully halogenated where possible;
or a pharmaceutically acceptable salt thereof.

[0007] In another embodiment 2, the invention provides compounds of the formula (I) according to the embodiment immediately above, and wherein

ring A is

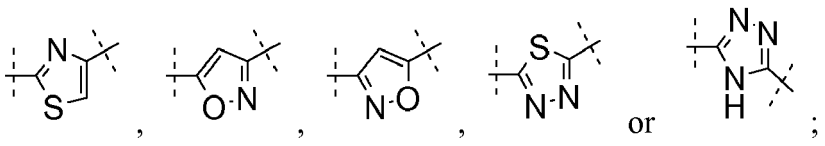


R^2 is C_{1-6} alkyl, C_{3-7} cycloalkyl, 1,1-dioxo-1λ^6-thiomorpholinylcarbonyl, phenylsulfonyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl or piperidinyl, each optionally independently substituted with 1 to 3 substituents chosen from C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{1-5} alkoxy, C_{1-5} alkylthio, C_{1-5} alkylsulfonyl, C_{1-5} alkoxycarbonyl, C_{1-5} alkylamino, C_{3-6} cycloalkylamino, C_{1-5} dialkylamino, C_{1-5} alkylaminocarbonyl, C_{1-5} acylamino, C_{1-5} dialkylaminocarbonyl, hydroxyl, halogen, cyano, nitro, oxo, phenyl and heterocyclyl chosen from tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl and piperazinyl,
each R^2 substituent where possible is optionally halogenated or substituted with 1 to 3 C_{1-5} alkyl, C_{1-5} acyl, methyl sulfonyl, cyano, phenyl, oxo or hydroxyl;
or **R^1** and **R^2** together with the nitrogen atom to which they are attached form a ring chosen from thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, benzimidazolyl, pyrazolyl, imidazolyl, triazinyl, indazolyl, indolyl, indolinyl, isoindolyl, isoindolinyl, and 2-aza-spiro[4.5]dec-2-yl, 1-aza-spiro[4.5]dec-1-yl, 1-aza-spiro[4.4]non-1-yl, 2-aza-spiro[4.4]non-2-yl, 2-aza-spiro[5.5]undec-2-yl, 1-aza-spiro[5.5]undec-1-yl
each optionally substituted with 1 to 3 C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkyl sulfonyl, cyano, phenyl, oxo, hydroxyl and halogen each ring substituent being further optionally halogenated where possible;

R^3 and **$R^{3'}$** are each methyl or ethyl, each optionally halogenated, or R^3 and R^4 together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring each optionally halogenated.

[0008] In another embodiment 3, the invention provides compounds of the formula (I) according to the embodiment described immediately above, and wherein

ring A is



R^1 is hydrogen or C_{1-3} alkyl optionally halogenated;

R^2 is C_{1-6} alkyl or C_{3-7} cycloalkyl optionally independently substituted with 1 to 3 halogen, one C_{3-7} cycloalkyl, C_{1-6} alkoxy or one heterocyclyl chosen from tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl and piperazinyl each optionally halogenated or substituted with C_{1-4} alkyl or methyl sulfonyl;

or **R^1** and **R^2** together with the nitrogen atom to which they are attached form a ring chosen form thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, azetidinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, and 2-aza-spiro[4.5]dec-2-yl each optionally substituted with 1 to 3 C_{1-4} alkyl, C_{1-4} alkoxy and halogen each ring substituent being further optionally halogenated where possible;

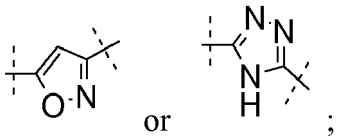
R^3 and **$R^{3'}$** are each methyl or ethyl or R^3 and R^4 together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring;

R6 is hydrogen or C_{1-2} alkyl;

R7 and **R8** are each C_{1-2} alkyl.

[0009] In another embodiment 4, the invention provides compounds of the formula (I) according to the embodiment immediately above, and wherein

ring A is



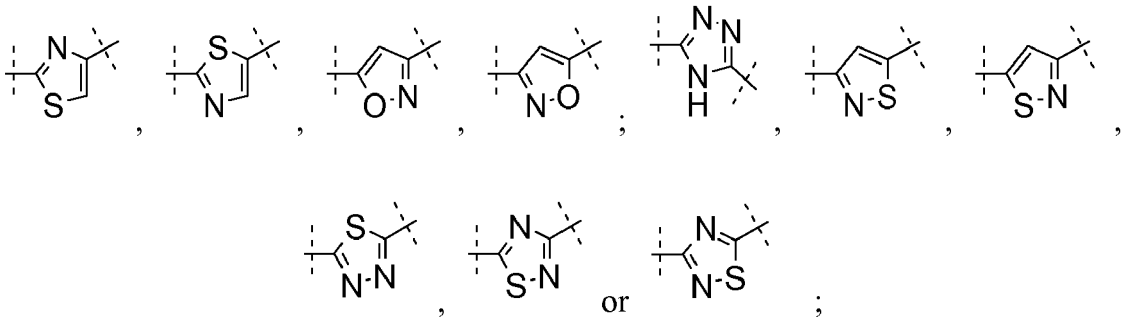
;

R2 is methyl optionally substituted with one heterocyclyl chosen from tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl and piperazinyl each optionally halogenated or substituted with C_{1-4} alkyl or methyl sulfonyl;

or **R1** and **R2** together with the nitrogen atom to which they are attached form a ring chosen form thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, azetidinyl, indolyl and 2-aza-spiro[4.5]dec-2-yl each optionally substituted with 1 to 3 C_{1-3} alkyl, C_{1-3} alkoxy and halogen each ring substituent being further optionally halogenated where possible.

[0010] In another embodiment 5, the invention provides compounds of the formula (I) according to the embodiment 1, and wherein

ring A is



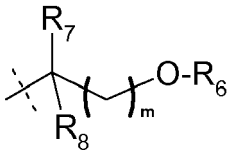
R1 is hydrogen, C_{1-6} alkyl or C_{3-7} cycloalkyl optionally substituted with 1-3 C_{1-6} alkyl,
each **R1** or it's substituent is optionally halogenated;

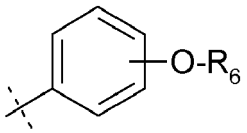
R2 is cyclopentyl, cyclohexyl, tetrahydropyranyl, tetrahydrofuranyl, thiomorpholinylcarbonyl, 1,1-dioxo-1λ^6-thiomorpholinylcarbonyl, morpho linylcarbonyl, phenylsulfonyl, phenylcarbonyl, phenyl, pyridinyl, piperidinyl, pyrimidinyl or thiazolyl, each optionally independently substituted with 1 to 3 substituents chosen from C_{1-5} alkyl, C_{3-5} cycloalkyl, C_{1-5} alkoxy, C_{1-5} alkylthio, C_{1-5} alkylsulfonyl, C_{1-5} alkoxycarbonyl, C_{1-5} alkylamino, C_{3-6} cycloalkylamino, C_{1-5} dialkylamino, C_{1-5} alkylaminocarbonyl, C_{1-5} acylamino, C_{1-5} dialkylaminocarbonyl, hydroxyl, halogen, cyano and nitro, each **R2** substituent where possible is optionally halogenated or substituted with 1 to 3 C_{1-5} alkyl or C_{1-5} alkyl sulfonyl, or **R1** and **R2** together with the nitrogen atom to which they are attached form a ring chosen from tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, benzimidazolyl, pyrazolyl, imidazolyl, triazinyl, indazolyl, indolyl, indolinyl, isoindolyl, isoindolinyl, and 2-aza-spiro[4.5]dec-2-yl, 1-aza-spiro[4.5]dec-1-yl, 1-aza-spiro[4.4]non-1-yl, 2-aza-spiro[4.4]non-2-yl, 2-aza-spiro[5.5]undec-2-yl, 1-aza-spiro[5.5]undec-1-yl
each optionally substituted with 1 to 3 C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkyl sulfonyl, cyano, phenyl, oxo, hydroxyl or halogen each ring substituent being further optionally halogenated where possible;

R3 and **R3'** are each methyl optionally halogenated , or R^3 and $R^{3'}$ together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring each optionally halogenated;

R4 is hydrogen;

R5 is chosen from



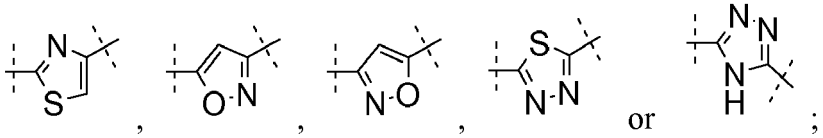
, and


;

R6 is hydrogen or C_{1-3} alkyl;
wherein **R7** and **R8** are each C_{1-3} alkyl or C_{3-6} cycloalkyl.

[0011] In another embodiment 6, the invention provides compounds of the formula (I) according to the embodiment 3, and wherein

ring A is



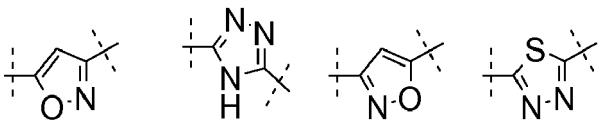
or
;

R3 and **R3'** are methyl;

R6 is hydrogen or C_{1-2} alkyl;
wherein **R7** and **R8** are each C_{1-2} alkyl.

[0012] In another embodiment 7, the invention provides compounds of the formula (I) according to the embodiment 6, and wherein

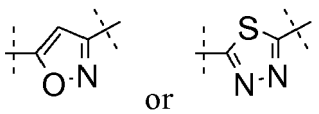
ring A is



R1 and **R2** together with the nitrogen atom to which they are attached form a ring chosen from thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, azetidinyl, indolyl and 2-aza-spiro[4.5]dec-2-yl each optionally substituted with 1 to 3 C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy and halogen each ring substituent being further optionally halogenated where possible.

[0013] In another embodiment 8, the invention provides compounds of the formula (I) according to the embodiment described immediately above, and wherein

ring A is



or
.

[0014] In another embodiment 9, the invention provides compounds of the formula (I) according to the embodiment described immediately above, and wherein

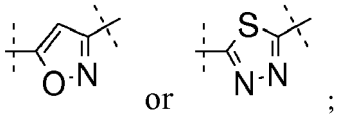
R^1 and **R^2** together with the nitrogen atom to which they are attached form a ring chosen from morpholinyl, pyrrolidinyl and piperidinyl, each optionally substituted with 1 to 3 C_{1-3} alkyl.

[0015] In another embodiment 10, the invention provides compounds of the formula (I) according to embodiment 2, and wherein

R^2 is cyclopropyl, cyclohexyl, tetrahydropyranyl, pyrrolidinyl or piperidinyl, each optionally independently substituted with 1 to 2 substituents chosen from C_{1-3} alkyl and C_{1-2} alkylsulfonyl.

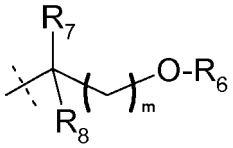
[0016] In another embodiment 11, the invention provides compounds of the formula (I) according to embodiment 2, and wherein

R^2 is CF_3-CH_2-CH_2-CH_2-, CH_3-CH_2-$CH_2(CH_3)$-, cyclopropyl-CH_2-, hydroxylcyclohexyl, tetrahydrofuranyl-CH_2-, ring A is



;

R^5 is

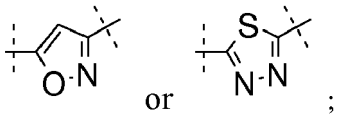


wherein
wherein **R^7** and **R^8** optionally can cyclize to form a C_{3-7} cycloalkyl ring.

[0017] In another embodiment 12, the invention provides compounds of the formula (I) according to embodiment 2, and wherein

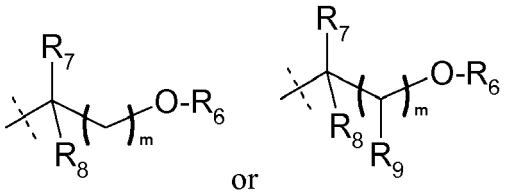
R^2 hydroxylcyclohexyl, tetrahydropyranyl, hydroxylpyrrolidinyl or methylsulfonylpyrrolidinyl;

ring A is



;

R^5 is

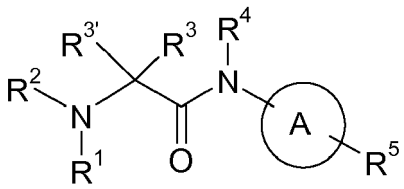


wherein
wherein **R^7** and **R^8** optionally can cyclize to form a C_{3-7} cycloalkyl ring;

R^1 and R^2 optionally can cyclize to form piperidinyl, methylsulfonylpiperidinyl.

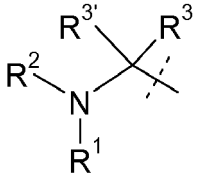
[0018] In another aspect of the invention there is provided a second set of generic embodiments, wherein for each of the above embodiments 1-10 of the formula (I), R^7 and R^6 can cyclize to form a 4-6 membered heterocyclic ring.

[0019] In another embodiment there is provided a compound of the formula (II)

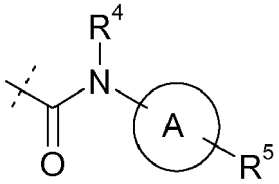


(II)

wherein

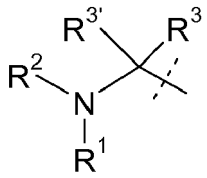
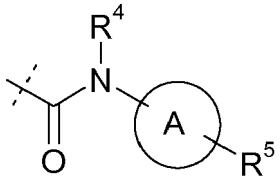
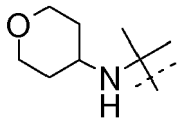
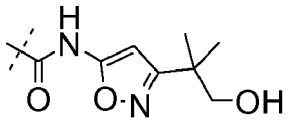
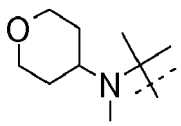
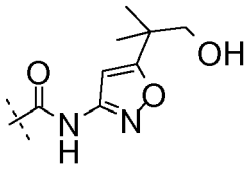


of the formula (I) is chosen from column A1 - A42 in Table I, and



of the formula (I) is chosen from column B1 - B22 in Table I, with the proviso that when column B is B3, B13 or B22, then A must be A20, A23, A38, or A42

Table I

			
A1		B1	
A2		B2	

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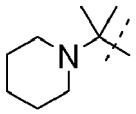
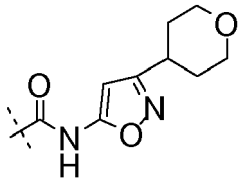
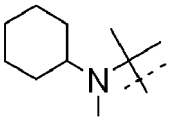
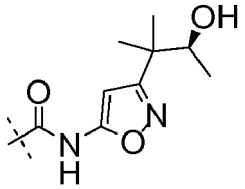
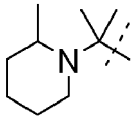
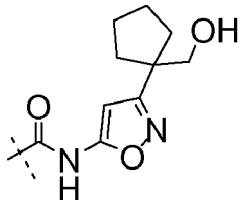
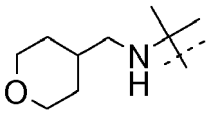
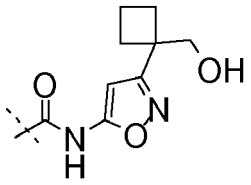
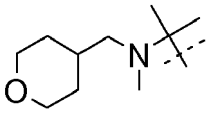
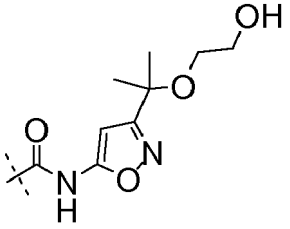
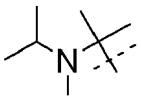
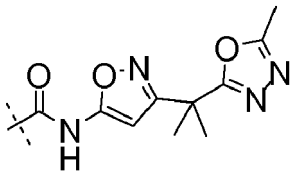
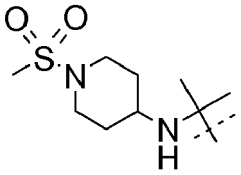
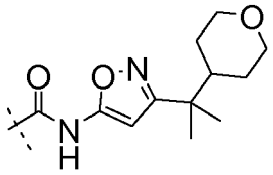
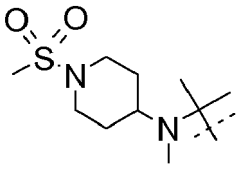
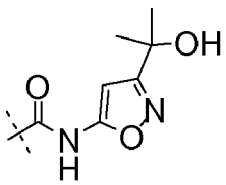
A3		B3	
A4		B4	
A5		B5	
A6		B6	
A7		B7	
A8		B8	
A9		B9	
A10		B10	

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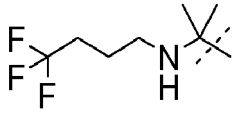
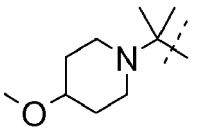
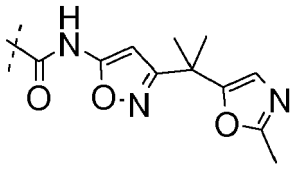
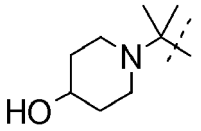
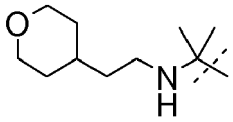
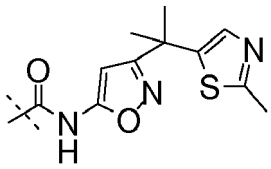
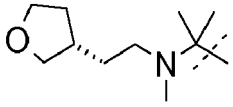
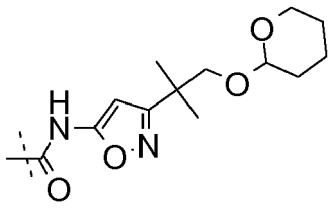
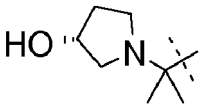
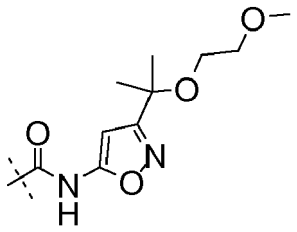
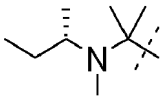
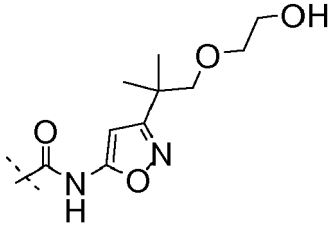
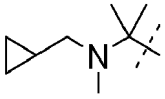
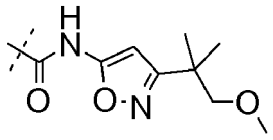
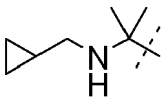
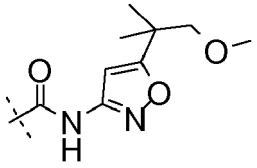
A11			
A12		B12	
A13			
A14		B14	
A15		B15	
A16		B16	
A17		B17	
A18		B18	
A19		B19	

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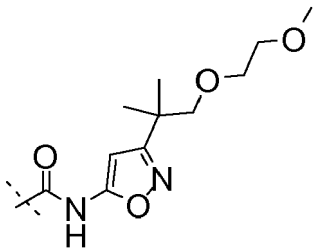
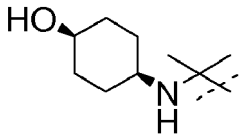
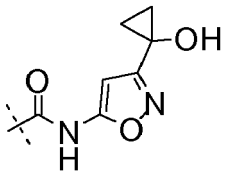
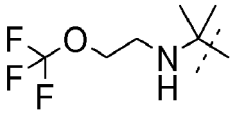
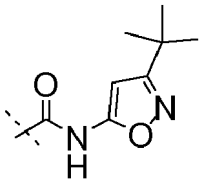
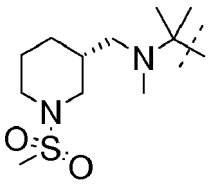
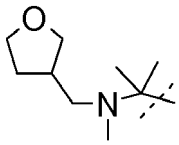
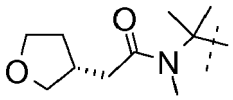
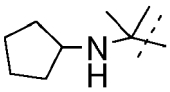
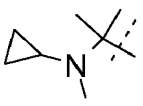
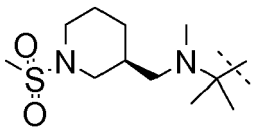
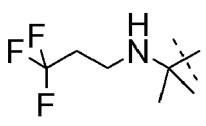
		B20	
A21		B21	
A22		B22	
A24			
A25			
A26			
A27			
A28			
A29			
A30			

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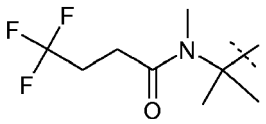
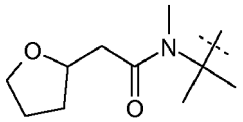
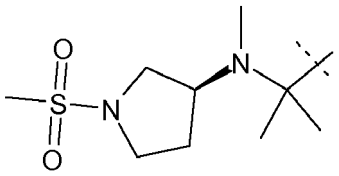
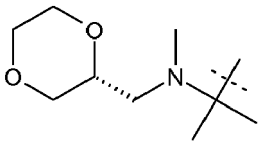
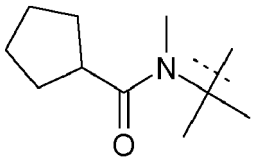
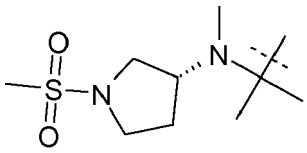
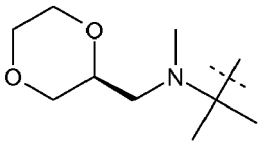
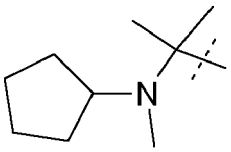
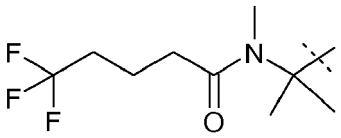
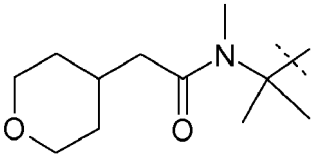
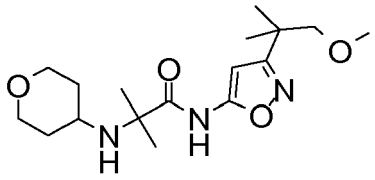
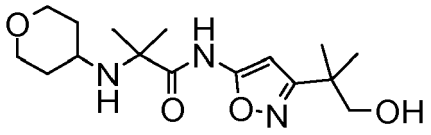
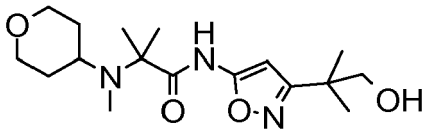
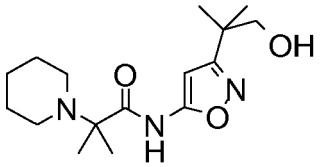
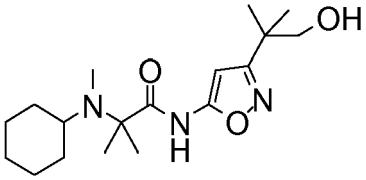
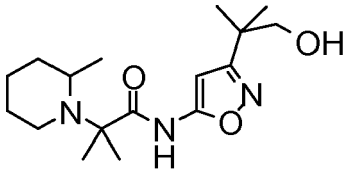
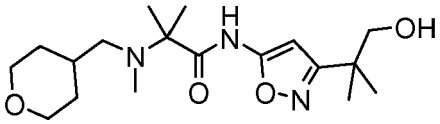
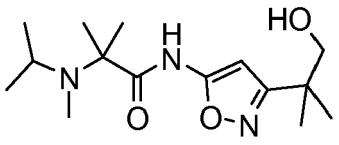
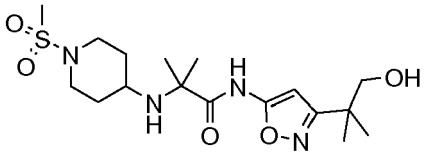
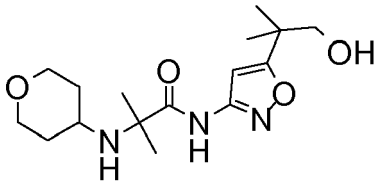
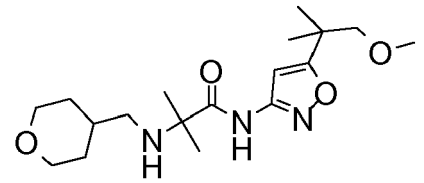
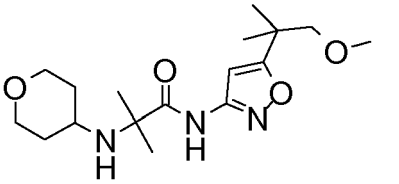
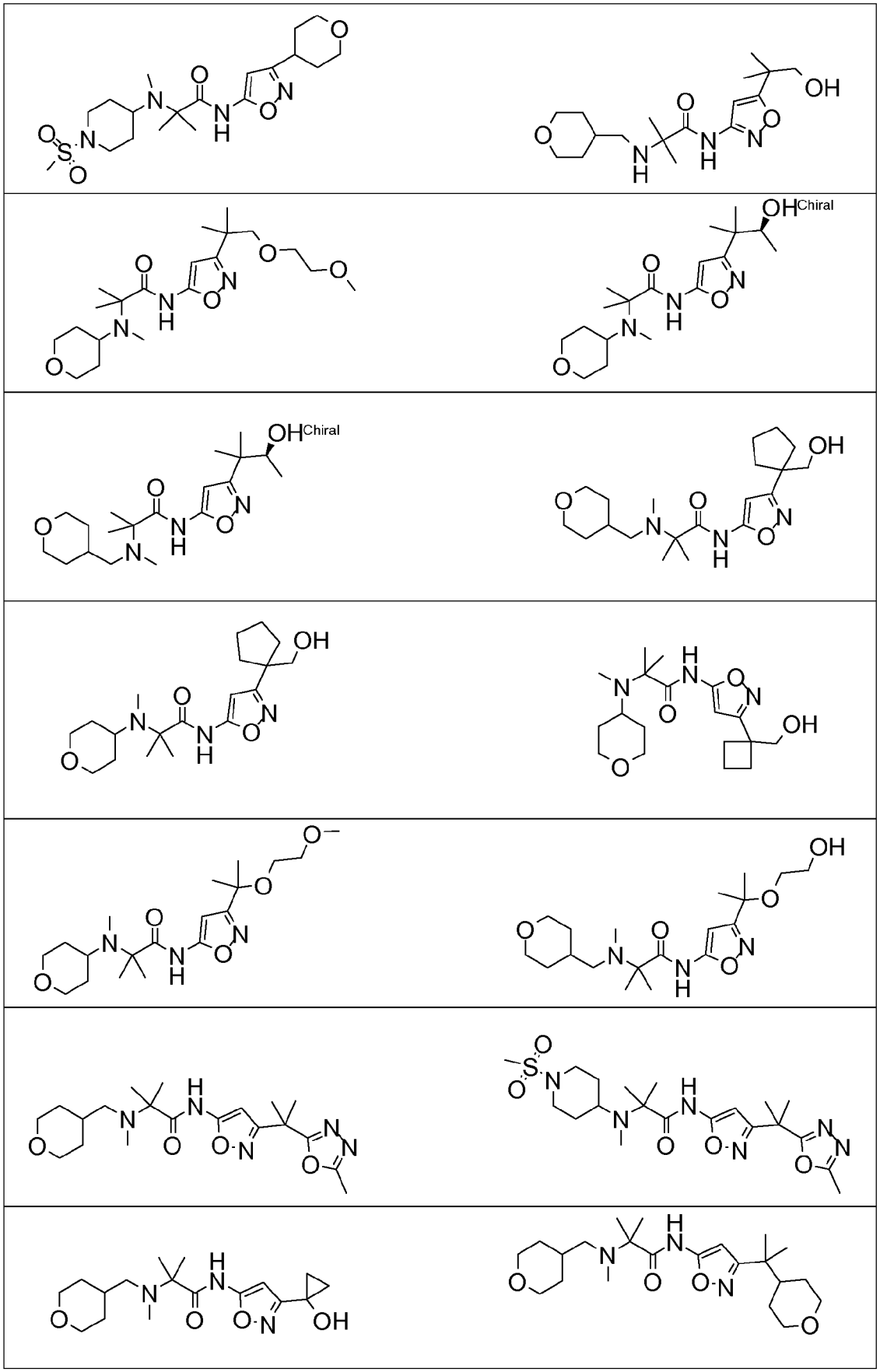
A31			
A32			
A33			
A34			
A35			
A36			
A37			
A39			
A40			
A41			

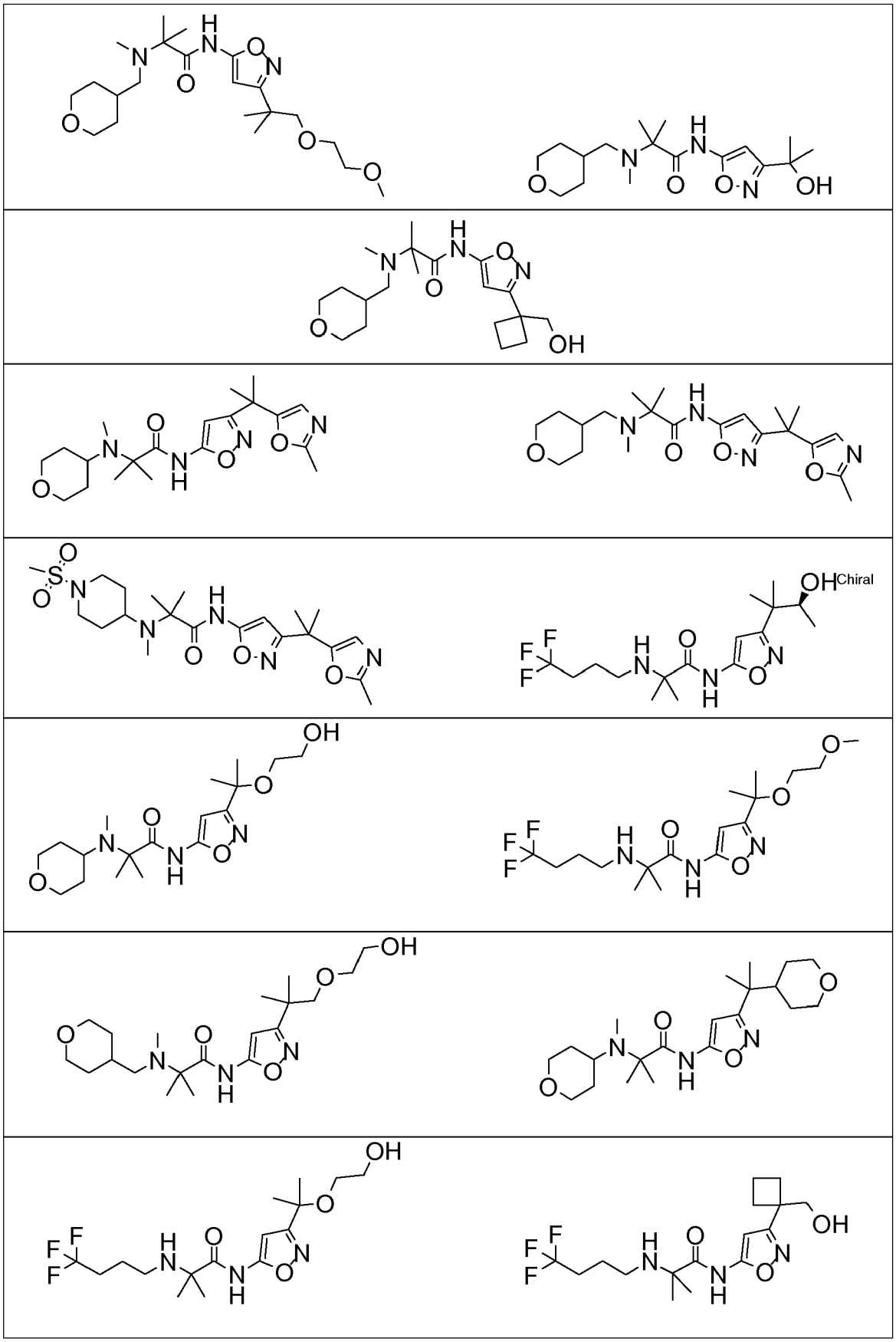
[0020] In another embodiment, the invention provides made compounds in Table II which can be made in view of the

general schemes, examples and methods known in the art.

Table II

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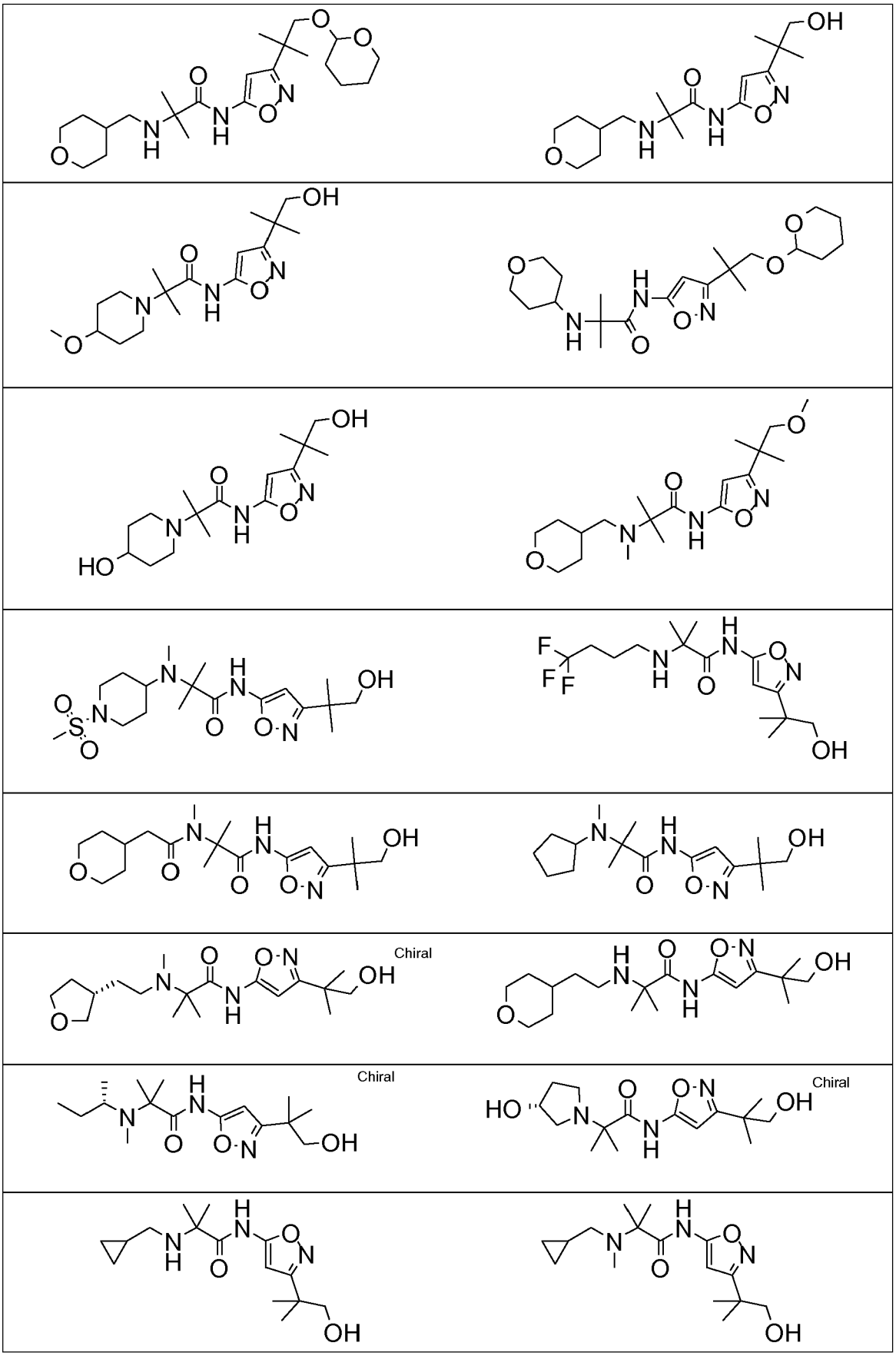
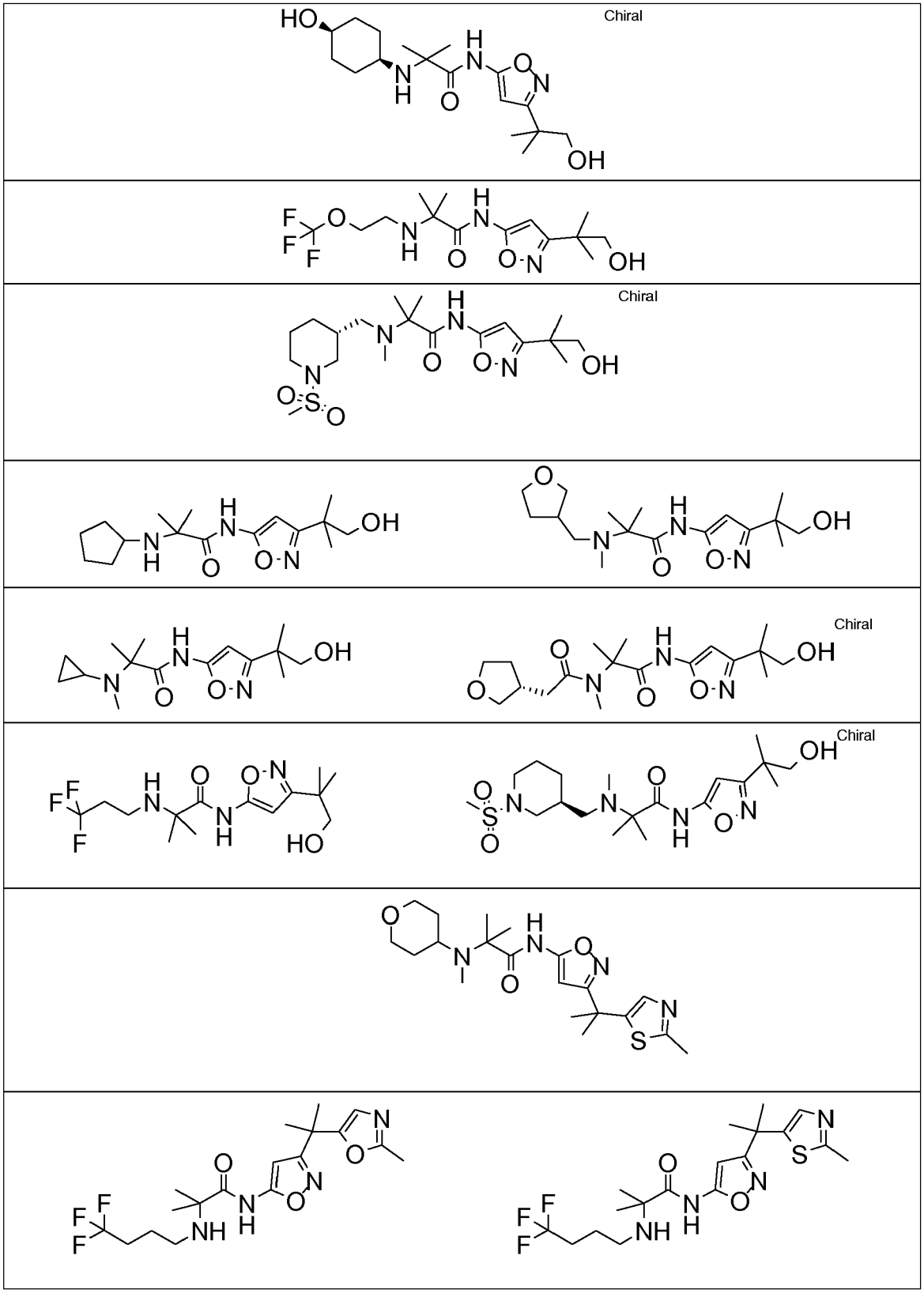
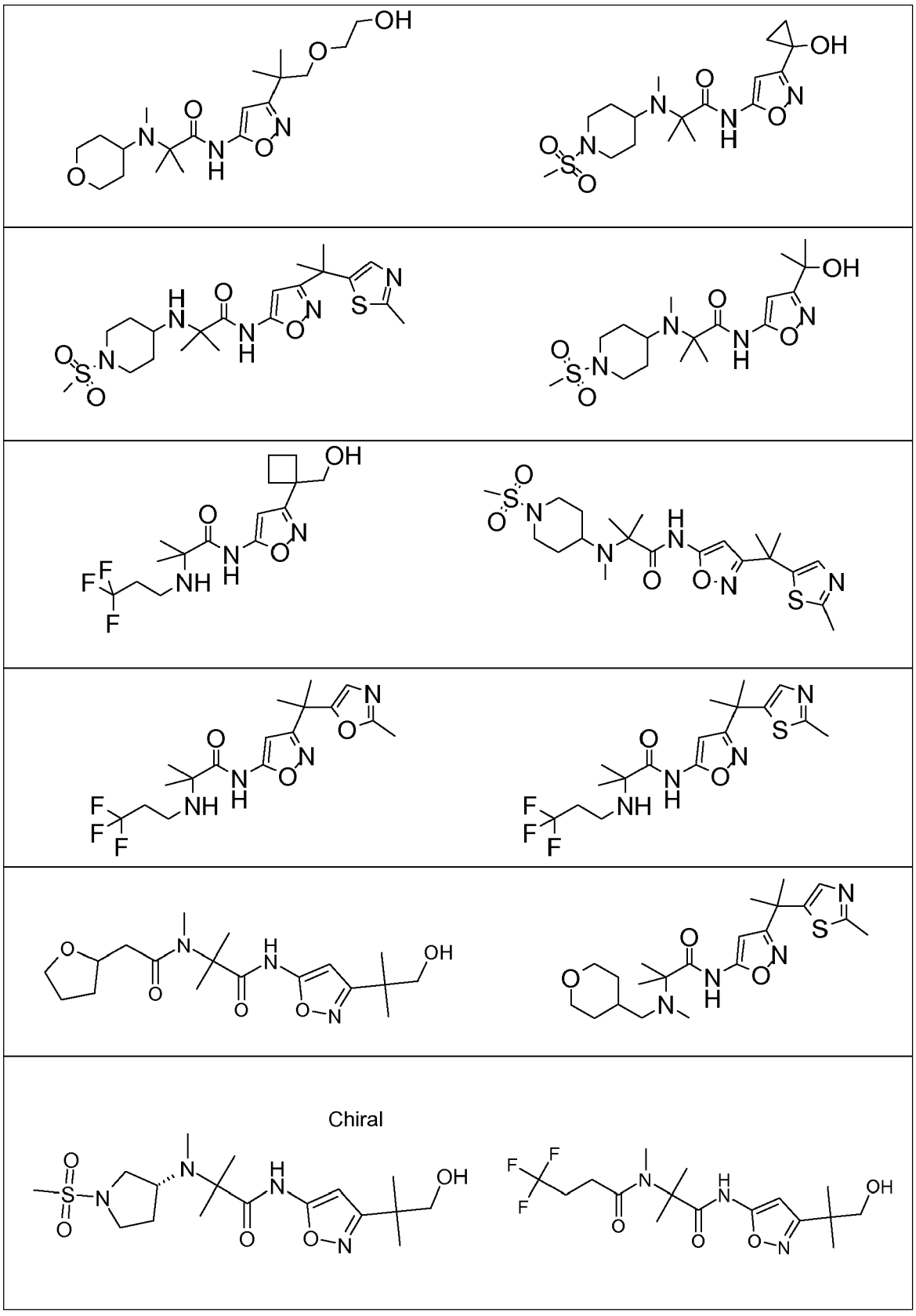
Chiral




Chiral
Chiral
Chiral
Chiral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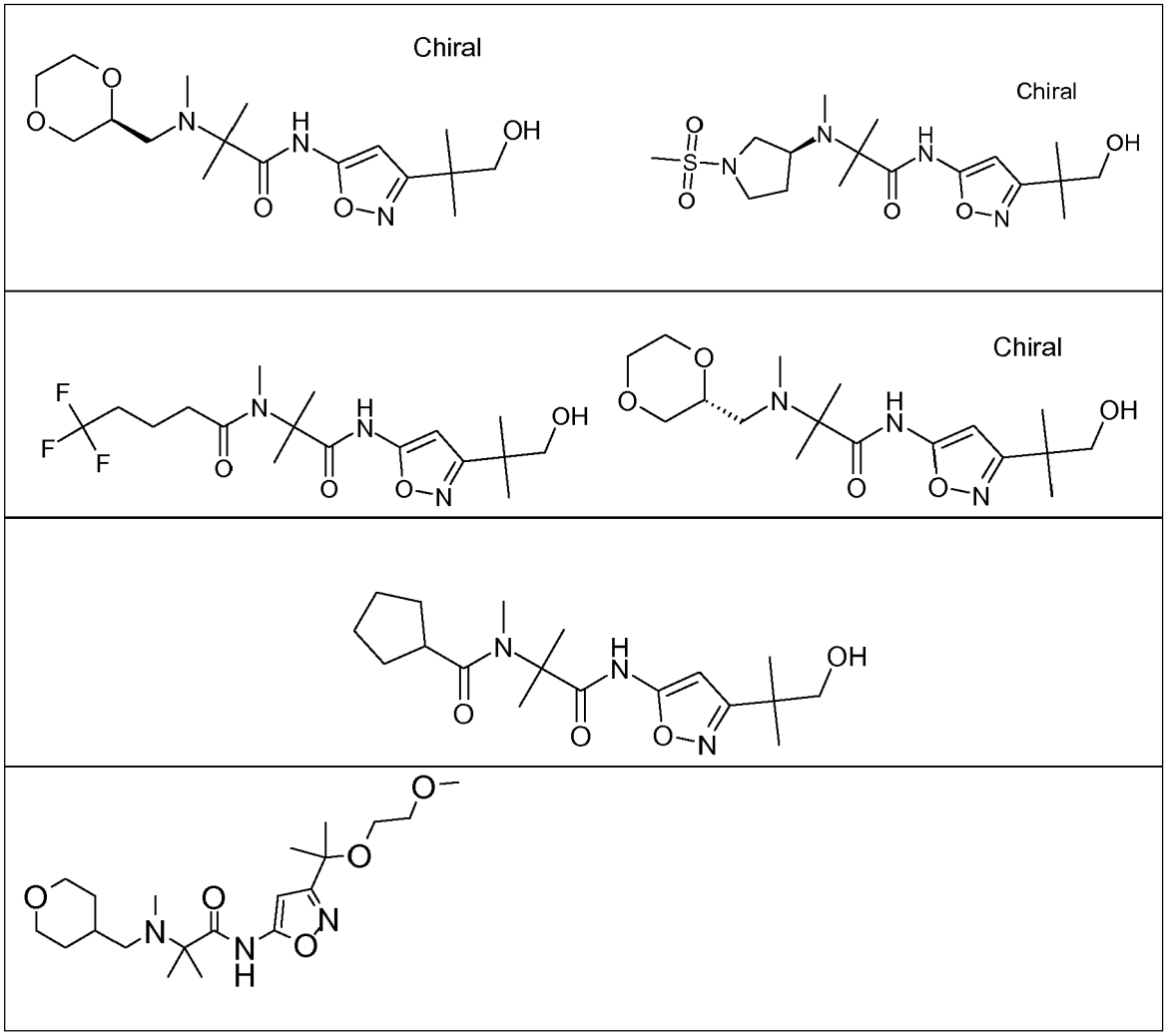
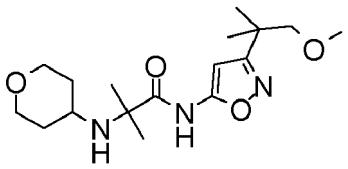
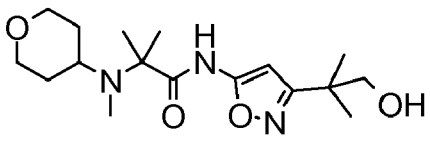
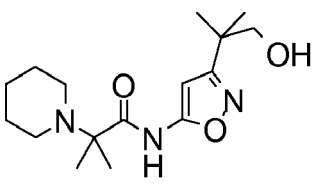


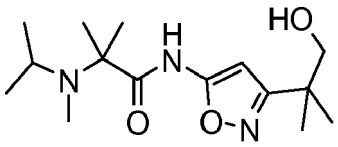
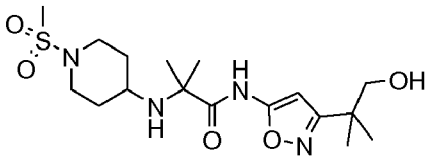
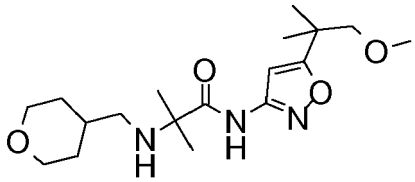
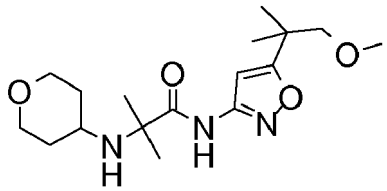
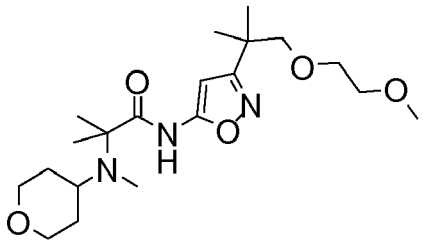
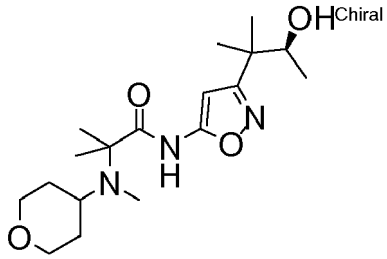
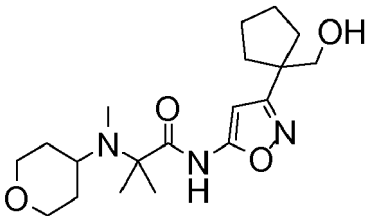
or a pharmaceutically acceptable salt thereof.

[0021] Of the above compounds, the following are preferred CB2 agonists:

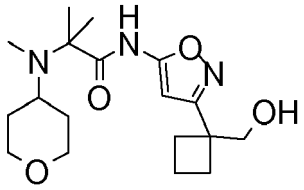
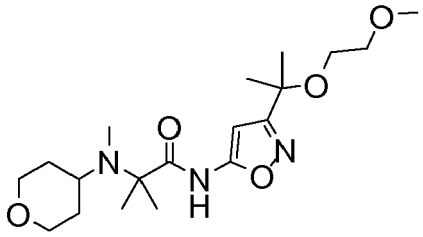
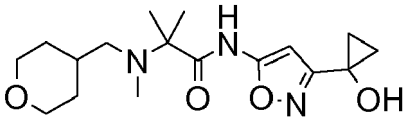
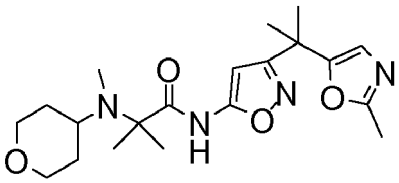
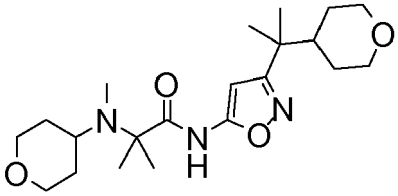
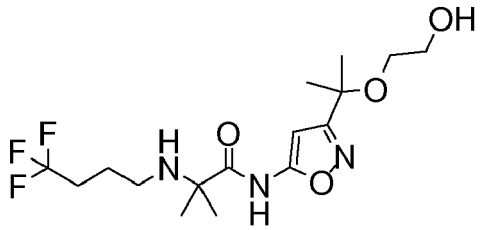
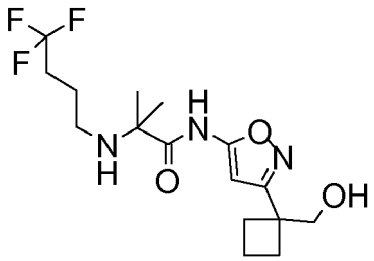
Table III

Compound	CB2 EC_{50} (nM)	CB1 EC_{50} (nM)
	313	>20000
	56	>50000
	28	22037

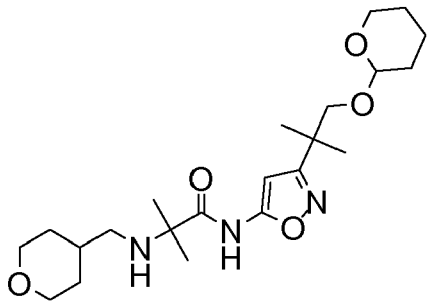
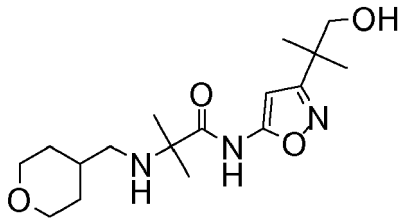
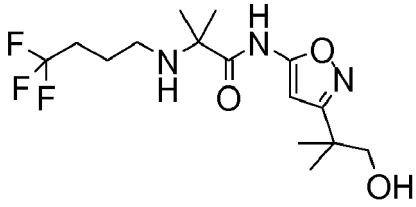
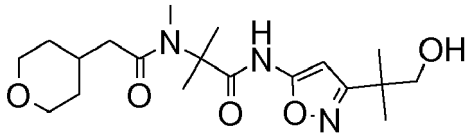
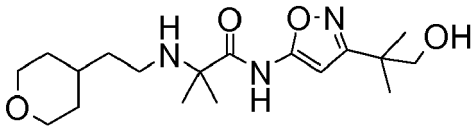
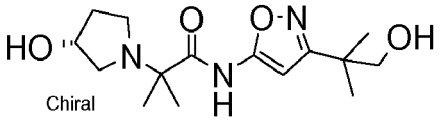
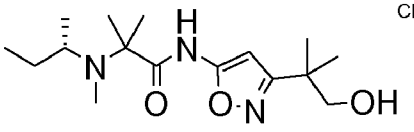
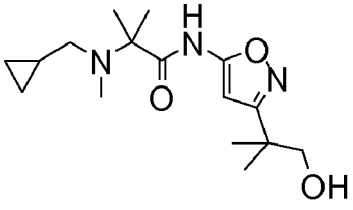
(continued)

Compound	CB2 EC_{50} (nM)	CB1 EC_{50} (nM)
	244	>50000
	302	>50000
	132	>20000
	337	>20000
	246	>50000
	28	44747
	21	21534

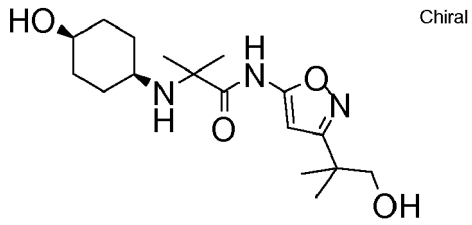
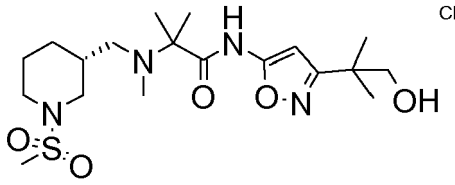
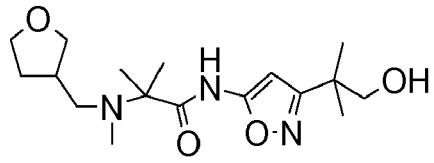
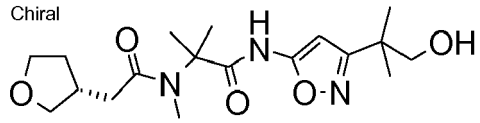
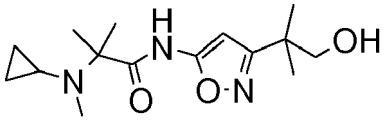
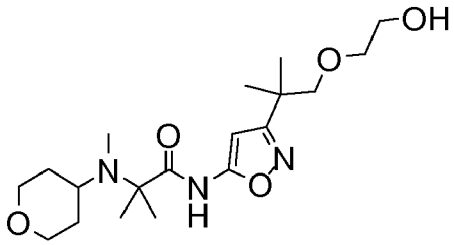
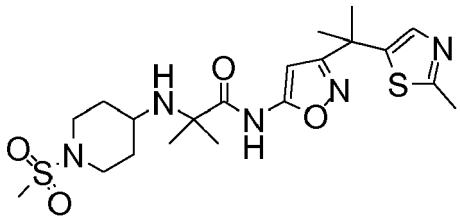
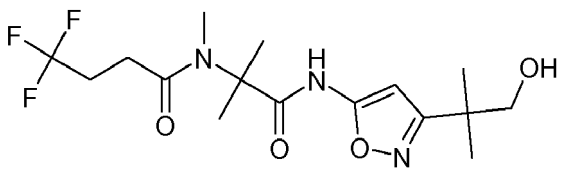
(continued)

Compound	CB2 EC_{50} (nM)	CB1 EC_{50} (nM)
	66	>50000
	93	>50000
	13	>50000
	15	20819
	44	>50000
	109	>50000
	54	>50000

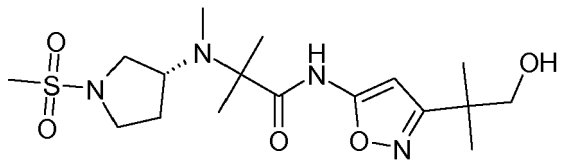
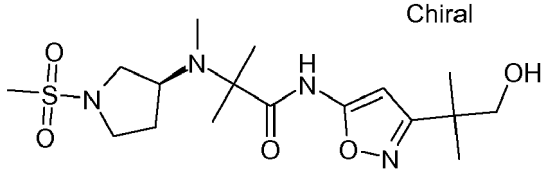
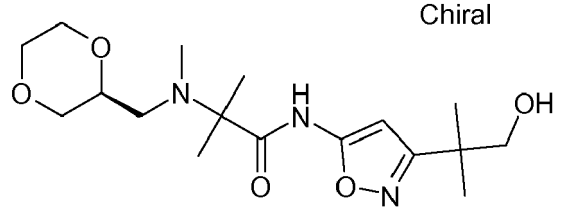
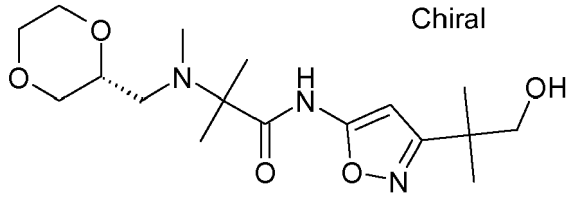
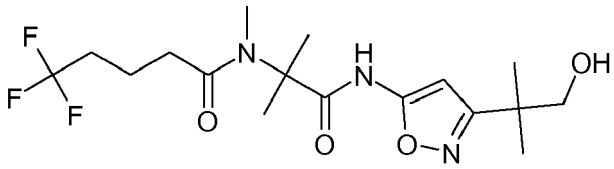
(continued)

Compound	CB2 EC_{50} (nM)	CB1 EC_{50} (nM)
	201	> 50000
	374	> 50000
	31	> 50000
	27	> 50000
	113	> 50000
 Chiral	494	> 50000
 Chiral	220	> 50000
	12	36007

(continued)

Compound	CB2 EC_{50} (nM)	CB1 EC_{50} (nM)
 Chiral	300	> 50000
 Chiral	126	> 50000
	29	> 50000
 Chiral	25	> 50000
	446	nt
	15	37646
	195	> 50000
	69	> 50000

(continued)

Compound	CB2 EC_{50} (nM)	CB1 EC_{50} (nM)
Chiral 	1.7	>20000
Chiral 	28	> 50000
Chiral 	68	> 50000
Chiral 	40	> 50000
	27	32068

[0022] In all the compounds disclosed hereinabove in this application, in the event the nomenclature is in conflict with the structure, it shall be understood that the compound is defined by the structure.

[0023] The invention also relates to pharmaceutical preparations, containing as active substance one or more compounds of formula (I), or the pharmaceutically acceptable derivatives thereof, optionally combined with conventional excipients and/or carriers.

[0024] Compounds of the invention also include their isotopically-labelled forms. An isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.* ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

[0025] The invention includes the use of any compounds of described above containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Isomers shall be defined as being enantiomers and diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

[0026] Some of the compounds of formula (I) can exist in more than one tautomeric form. The invention includes methods using all such tautomers.

[0027] All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C_{1-4}alkoxy" is a C_{1-4}alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, butoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

[0028] Carbocycles include hydrocarbon rings containing from three to twelve carbon atoms. These carbocycles may be either aromatic either aromatic or non-aromatic ring systems. The non-aromatic ring systems may be mono- or polyunsaturated. Preferred carbocycles include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl, decahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl. Certain terms for cycloalkyl such as cyclobutanyl and cyclobutyl shall be used interchangeably. The term "heterocycle" refers to a stable nonaromatic 4-8 membered (but preferably, 5 or 6 membered) monocyclic or nonaromatic 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated. Each heterocycle consists of carbon atoms and one or more, preferably from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. The term "heteroaryl" shall be understood to mean an aromatic 5-8 membered monocyclic or 8-11 membered bicyclic ring containing 1-4 heteroatoms such as N,O and S.

[0029] Unless otherwise stated, heterocycles and heteroaryl include but are not limited to, for example benzoxazolyl, benzothiazolyl, benzimidazolyl, tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, pyrrolyl, imidazolyl, thienyl, thiadiazolyl, triazolyl, thiomorpholinyl, 1,1-Dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, pyrrolidinyl, piperidinyl, piperazinyl, purinyl, quinolinyl, Dihydro-2H-quinolinyl, isoquinolinyl, quinazolinyl, indazolyl, thieno[2,3-d]pyrimidinyl, indolyl, isoindolyl, benzofuranyl, benzopyranyl and benzodioxolyl.

[0030] The term "heteroatom" as used herein shall be understood to mean atoms other than carbon such as O, N, S and P.

[0031] In all alkyl groups or carbon chains one or more carbon atoms can be optionally replaced by heteroatoms: O, S or N, it shall be understood that if N is not substituted then it is NH, it shall also be understood that the heteroatoms may replace either terminal carbon atoms or internal carbon atoms within a branched or unbranched carbon chain. Such groups can be substituted as herein above described by groups such as oxo to result in defintions such as but not limited to: alkoxycarbonyl, acyl, amido and thioxo.

[0032] The term "aryl" as used herein shall be understood to mean aromatic carbocycle or heteroaryl as defined herein. Each aryl or heteroaryl unless otherwise specified includes it's partially or fully hydrogenated derivative. For example, quinolinyl may include decahydroquinolinyl and tetrahydroquinolinyl, naphthyl may include its hydrogenated derivatives such as tetrahydronaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

[0033] As used herein, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen.. For example, for an -S-C_{1-6} alkyl radical, unless otherwise specified, this shall be understood to include -S(O)-C_{1-6} alkyl and -$S(O)_2$-C_{1-6} alkyl.

[0034] The term "halogen" as used in the present specification shall be understood to mean bromine, chlorine, fluorine or iodine, preferably fluorine. The definitions "partially or fully halogenated"; partially or fully fluorinated; "substituted by one or more halogen atoms", includes for example, mono, di or tri halo derivatives on one or more carbon atoms. For alkyl, a nonlimiting example would be -CH_2CHF_2, -CF_3 etc.

[0035] The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the inventive methods disclosed herein.

[0036] The invention includes pharmaceutically acceptable derivatives of compounds of formula (I). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound useful for the invention, or a pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound of the invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the formula (I).

[0037] Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include

alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C_1-C_4 alkyl)$_4^+$ salts.

[0038] In addition, within the scope of the invention is use of prodrugs of compounds of the formula (I). Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug is administered to a patient, the prodrug may be transformed into a compound disclosed hereinabove, thereby imparting the desired pharmacological effect.

[0039] The compounds of formula I may be made using the general synthetic methods described below, which also constitute part of the invention.

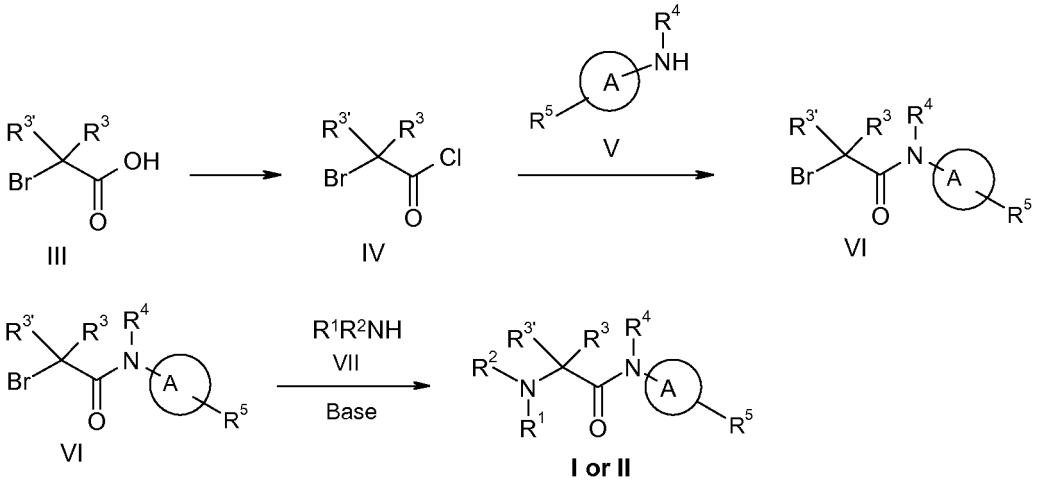
GENERAL SYNTHETIC METHODS

[0040] The invention also provides processes for making compounds of Formula (I) or Formula (II). In all Schemes, unless specified otherwise, R^1, R^2, R^3, $R^{3'}$, R^4, R^5 and A in the Formulas below shall have the meaning of R^1, R^2, R^3, $R^{3'}$, R^4, R^5 and A in Formula (I) or Formula (II) of the invention described herein above.

[0041] Optimum reaction conditions and reaction times may vary depending on the particular reactants used. Unless otherwise specified, solvents, temperatures, pressures, and other reaction conditions may be readily selected by one of ordinary skill in the art. Specific procedures are provided in the Synthetic Examples section. Typically, reaction progress may be monitored by thin layer chromatography (TLC), if desired, and intermediates and products may be purified by chromatography on silica gel and/or by recrystallization.

[0042] The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials and intermediates used, in the Schemes below, are either commercially available or easily prepared from commercially available materials by those skilled in the art.

[0043] The compounds of Formula (I) or Formula (II) may be synthesized according to Scheme 1:

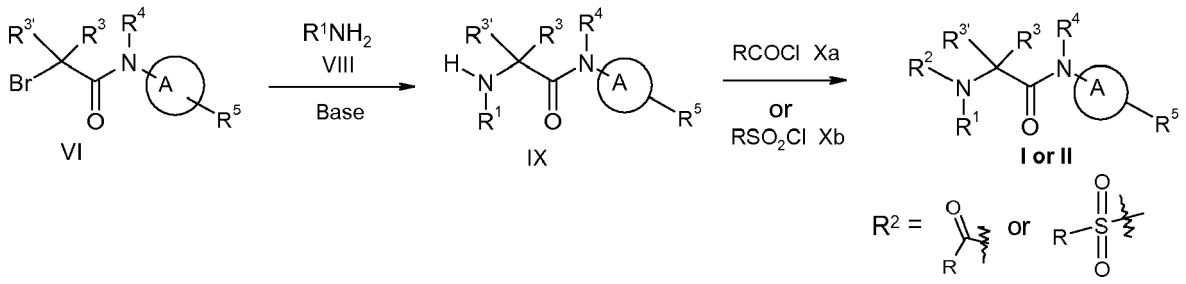


Scheme 1

[0044] As illustrated in scheme 1, reaction of an acid of formula (III) with reagents such as thionyl chloride or oxalyl chloride provides the corresponding acid chloride of formula (IV). Reaction of this acid chloride (IV) with an amine of formula (V), in a suitable solvent, in the presence of a suitable base such as N,N-diisopropylethylamine, provides an amide of formula (VI). Alternatively, the acid of formula (III) above may also be coupled with the corresponding amine of formula (V), under standard coupling conditions, to provide an amide of formula (VI). Standard peptide coupling reactions known in the art (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) may be employed in these syntheses. An example of suitable coupling conditions is treatment of a solution of the carboxylic acid in a suitable solvent such as DMF with EDC, HOBT, and a base such as diisopropylethylamine, followed by the desired amine.

[0045] Reaction of the intermediate of formula (VI) with an amine of formula (VII), in a suitable solvent, in the presence of a suitable base such as cesium carbonate, provides a compound of Formula (I) or Formula (II).

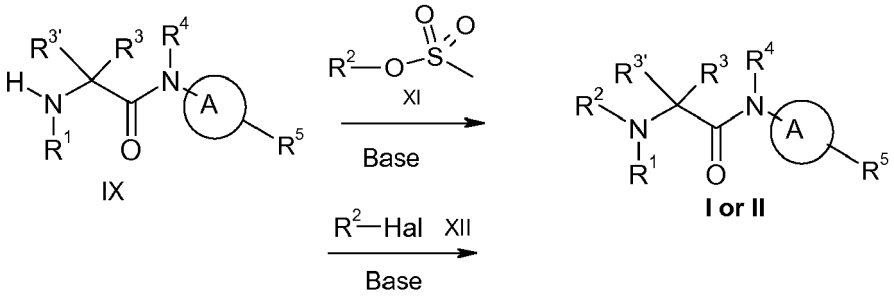
[0046] The compounds of Formula (I) or Formula (II) may be prepared according to Scheme 2:



Scheme 2

[0047] As outlined in scheme 2, reaction of an amide of formula (VI) with an amine of formula (VIII), in a suitable solvent, in the presence of a suitable base such as cesium carbonate, provides an amine of formula (IX). Reaction of the intermediate amine of formula (IX) with an acid chloride of formula (Xa) or a sulfonyl chloride of formula (Xb), in a suitable solvent, in the presence of a suitable base, provides a compound of Formula (I) or Formula (II) wherein R^2 = R-C(O)- or R-SO_2-

[0048] The compounds of Formula (I) or Formula (II) may be synthesized as outlined in Scheme 3:

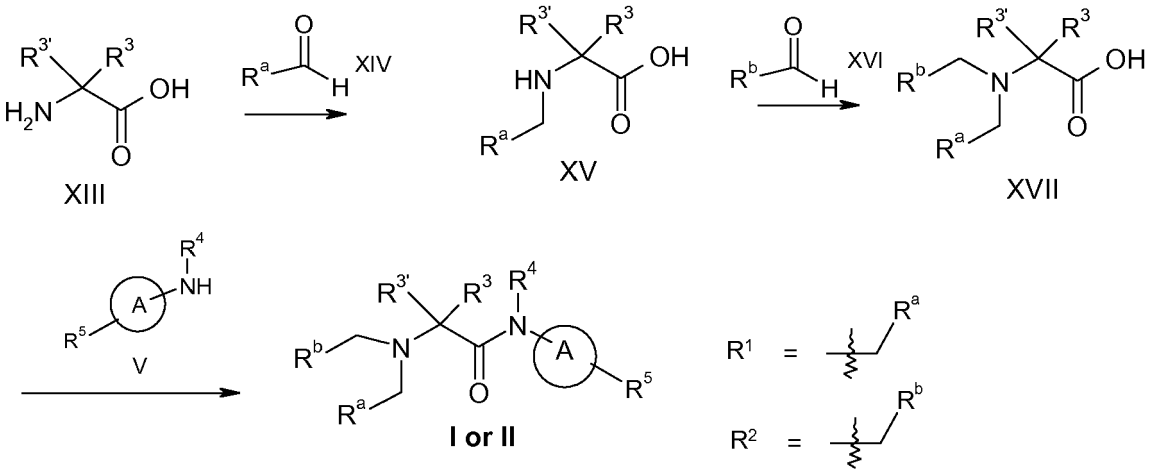


Scheme 3

[0049] As illustrated in scheme 3, reaction of an amine of formula (IX) with a compound of formula (XI), in a suitable solvent, in the presence of a suitable base such as cesium carbonate, provides a compound of Formula (I) or Formula (II)

[0050] Alternatively, reaction of an amine of formula (IX) with a compound of formula (XII) wherein Hal = bromo or iodo, in a suitable solvent, in the presence of a suitable base such as sodium hydride, provides a compound of Formula (I) or Formula (II) .

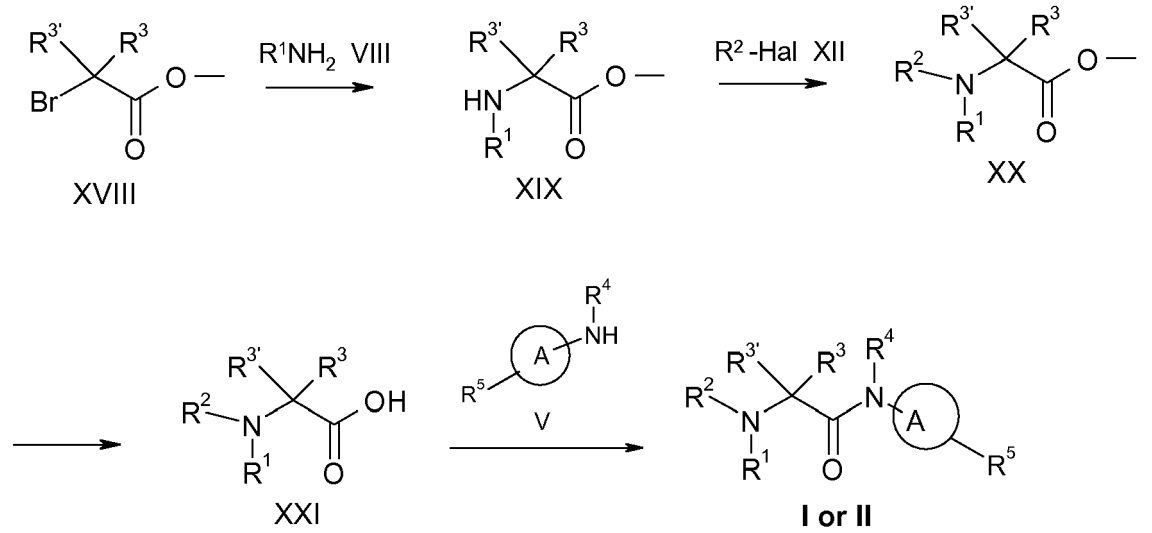
[0051] The compounds of Formula (I) or Formula (II) may be synthesized as shown in Scheme 4:



Scheme 4

[0052] As shown in scheme 4, reaction of an amino acid of formula (XIII) with an aldehyde of formula (XIV), under standard reductive amination conditions, provides an amine of formula (XV). Further reaction of amine of formula (XV) with an aldehyde of formula (XVI) provides the corresponding amine of formula (XVII). Coupling the intermediate of formula (XVII) with an amine of formula (V), as in scheme 1, provides a compound of Formula (I) or Formula (II) wherein $R^1 = R^a\text{-}CH_2\text{-}$ and $R^2 = R^b\text{-}CH_2\text{-}$

[0053] The compounds of Formula (I) or Formula (II) may be synthesized according to Scheme 5:



Scheme 5

[0054] As illustrated above in scheme 5, reaction of a bromo ester of formula (XVIII) with an amine of formula (VIII), in a suitable solvent, provides the corresponding N-substituted product of formula (XIX). Reaction of the compound (XIX) with a halide of formula (XII), in a suitable solvent, in the presence of a suitable base, provides a tertiary amine of formula (XX). Ester hydrolysis under standard conditions provides an acid of formula (XXI). Coupling the acid formula (XXI) with an amine of formula (V), as in scheme 1, provides a compound of Formula (I) or Formula (II).

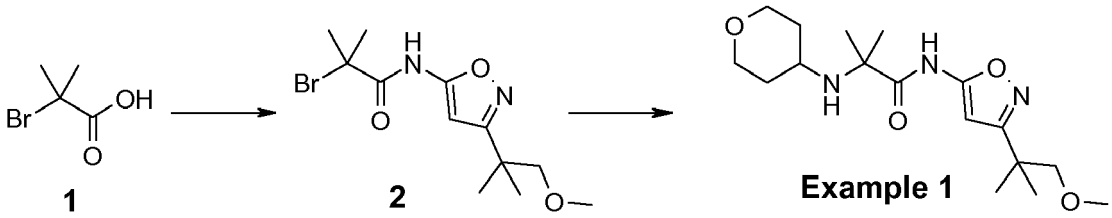
[0055] Further modification of the initial product of Formula (I) or Formula (II), by methods known in the art and illustrated in the Examples below, may be used to prepare additional compounds of this invention.

EXAMPLES:

Method A

Synthesis of Example 1

[0056]



Step 1: Synthesis of compound 2

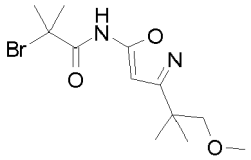
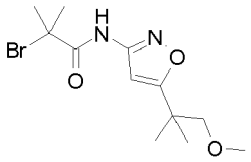
[0057] To a flask containing 2-bromo-2-methyl-propionic acid (1) (0.6 g, 3.5 mmol) under nitrogen is added thionyl chloride (2 mL). The reaction mixture is heated to 70 °C where it is maintained for 2 h. After this time, the reaction is cooled to room temperature and concentrated under reduced pressure. The crude acid chloride is used without further purification.

[0058] The crude acid chloride is dissolved in dichloromethane (DCM) (5 mL) and N,N-diisopropylethylamine (1 mL, 5.7 mmol) is added followed by 3-(2-methoxy-1,1-dimethyl-ethyl)-isoxazol-5-ylamine (0.6 g, 3.5 mmol).

[0059] The reaction is stirred for 16 h at room temperature. After this time, additional 2-bromo-2-methyl-propionic acid (0.3 g, 1.7 mmol) is activated as its acid chloride, as described above) and added to the reaction mixture. After further 1.5 h stirring, the mixture is washed with saturated aqueous $NaHCO_3$ solution (x 2), brine and the organic layer is separated, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product is purified by chromatography (silica, eluent: heptanes, 20% ethyl acetate) to provide compound 2 (0.6 g, 51 %);

[0060] According to the above procedure the following intermediates are synthesised:

Table 1:

Intermediate No.	Structure	Yield (%)	LC Method and Retention time [min]	m/z [M+H]
I (compound **2**)		51	LC Method b: 1.90	319/321
II		54	LC Method b: 1.96	319/321

Step 2: Synthesis of example 1

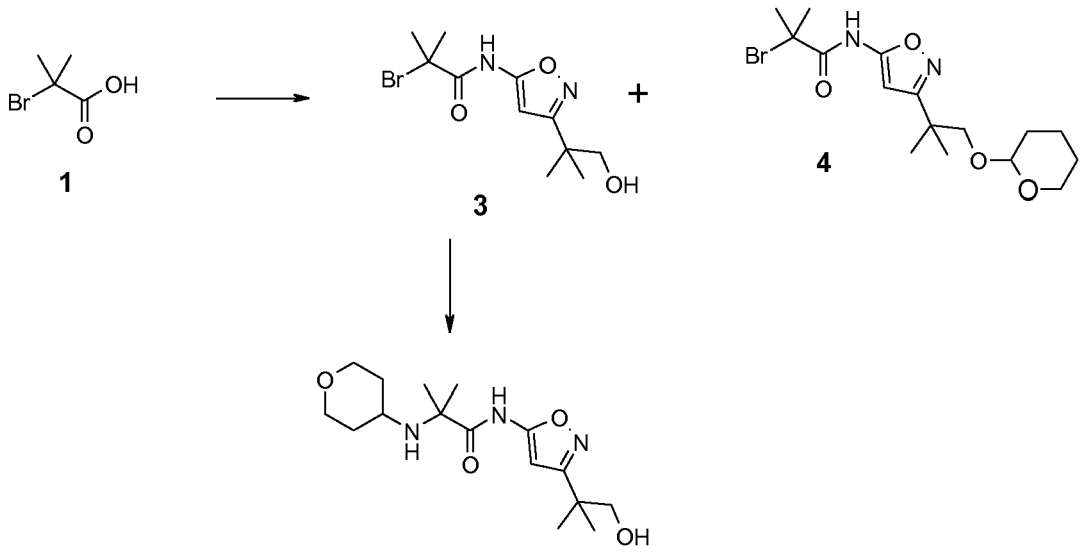
[0061] To a solution of 4-aminotetrahydropyran (0.1 g, 0.94 mmol) in THF (2 mL) are added Cs_2CO_3 (0.6 g, 1.84 mmol) and compound 2 (0.3 g, 0.94 mmol). The reaction is heated to 50 °C for 3 h. The solvent is then removed under reduced pressure and the residue is partitioned between DCM and 1M aqueous HCl solution. The acidic aqueous layer is basified with 5N aqueous NaOH solution and extracted with DCM (3 x 10 mL). The combined organic extracts are washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product is purified by column chromatography (silica, eluent: heptanes, 50% ethyl acetate) to yield example 1 (0.15 g, 41 %). LC-MS (LC Method a): retention time: 2.40 min, m/z 340 [M+H]

[0062] Compounds listed in Table IV under method A are made following this procedure.

Method B

Synthesis of Example 2

[0063]



Example 2

Step 1: Synthesis of compound 3

[0064] To a flask containing compound 1 (3 g, 18 mmol) under nitrogen is added thionyl chloride (6.6 mL). The reaction mixture is heated to 70 °C where it is maintained for 3 h. After this time, the reaction is cooled to room temperature and concentrated under reduced pressure. The crude acid chloride is used without further purification.

[0065] The crude acid chloride is dissolved in THF (11 mL) and N,N-diisopropylethylamine (3.1 mL , 18 mmol) is added, followed by 3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine (4.3 g, 18 mmol). The reaction is stirred for 16 h at 40 °C. The mixture is washed with saturated aqueous $NaHCO_3$ solution (x 2), brine and the organic layer is separated, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography (silica, eluent: heptanes, 20% ethyl acetate) allows separation and isolation of compound 3 (1 g, 18%), m/z 305/307 [$M+H^+$], from compound 4 (0.9 g, 13%), LC-MS (LC Method b): retention time: 2.35 min, m/z 411/413 [M+Na+H].

Step 2: Synthesis of example 2

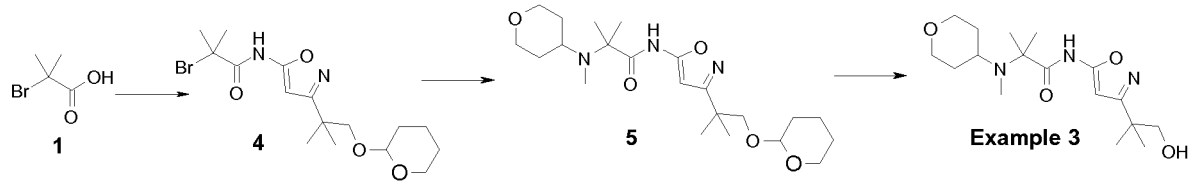
[0066] To a solution of 4-aminotetrahydropyran (0.05 g, 0.5 mmol) in THF (3 mL) are added Cs_2CO_3 (0.3 g, 1 mmol) and compound 3 (0.15 g, 0.5 mmol). The reaction is heated to 50 °C for 18 h. The solvent is then removed under reduced pressure and the residue is partitioned between DCM and 1M aqueous HCl solution. The acidic aqueous layer is basified with 5N aqueous NaOH solution and extracted with DCM (3 x 10 mL). The combined organic extracts are washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product is purified twice by column chromatography (silica, eluent: heptanes, 20% EtOAc) followed by trituration with 1M HCl in dioxane to yield the hydrochloride salt of example 2 (0.04 g, 22%). LC-MS (LC Method a): retention time: 2.16 min, m/z 326 [$M_{freebase}$+H]

[0067] Compounds listed in Table IV under method B are made following this procedure.

Method C

Synthesis of Example 3

[0068]



Step 1: Synthesis of compound 4

[0069] To a flask containing compound 1 (20.85 g, 125 mmol) in DCM (150 mL) under nitrogen is added oxalyl chloride (16.2 mL, 187.3 mmol), followed by DMF (5 drops). The reaction mixture is stirred at room temperature for 16 h and then concentrated under reduced pressure. The crude acid chloride, used without further purification, is dissolved in toluene (50 mL) and added dropwise over 10 min to a solution ofN,N-diisopropylethylamine (32.6 mL , 187 mmol) and 3-[1,1-dimethyl-2-(tetrahydro-pyran-2-yloxy)-ethyl]-isoxazol-5-ylamine (15 g, 62.4 mmol) in toluene (300 mL) at 50 °C. The reaction is stirred for 4 h at 60 °C. The reaction mixture is concentrated under reduced pressure and the residue is partitioned between DCM (300 mL) and water (250 mL). The organic layer is separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude orange oil is dissolved in diethyl ether and precipitated by addition of n-heptanes. The precipitate is isolated by filtration and washed sparingly with diethyl ether/heptanes to yield the first crop (9 g) of compound 4 as off-white solid. The mother liquor is concentrated and a second crop (3.3 g) is isolated by crystallisation/precipitation from diethyl ether/heptanes. The mother liquor is concentrated under reduced pressure and the residual orange oil filtered through silica (eluent: heptanes, 20% ethyl acetate), the filtrate is concentrated. The residue is dissolved in diethyl ether and the third crop (3.1 g) is isolated by diethyl ether/ heptanes treatment as described above. The combined yield of crop 1-3 is 15.4 g. Yield 63%; LC-MS (LC Method b): retention time: 2.35 min, m/z 411/413 [M+Na+H].

Step 2: Synthesis of compound 5

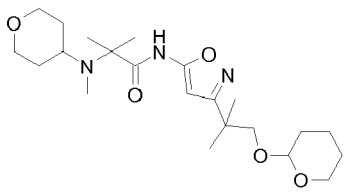
[0070] A solution of N-methyl-(tetrahydro-pyran-4-yl)-amine (0.25 g, 2.17 mmol), Cs_2CO_3 (1.41 g, 4.34 mmol) and compound 4 (0.85 g, 2.17 mmol) in THF (20 mL) is stirred at room temperature for 72 h. The reaction mixture is filtered through Celite ®, the solids are washed with ethyl acetate and DCM and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: heptanes, 50-100% ethyl acetate) to yield 374 mg of compound 5. Yield 41%;. LC-MS (LC Method b): retention time: 1.51 min, m/z 424 [M+H] The following amines are synthesised by adaptation of the above procedure with the following modification to be noted:
For intermediate II and III: excess of the corresponding amine (2.5 equ) and Cs_2CO_3 (2 equ.) are used, the work-up procedure includes a wash of the organic layer with 10 % aqueous citric acid solution followed by brine and the product is isolated by column chromatography (silica, eluent heptanes, 30% ethyl acetate).

[0071] For intermediate XI the reaction is stirred for 48 h at ambient temperature.

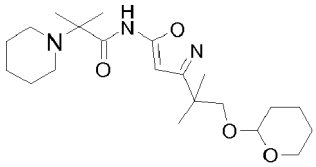
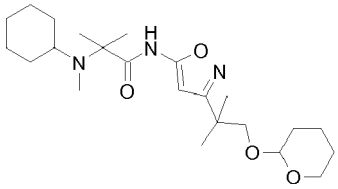
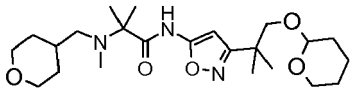
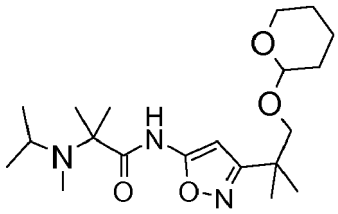
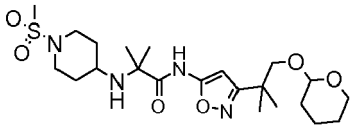
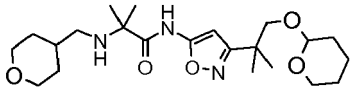
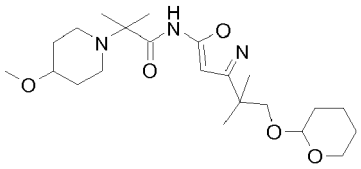
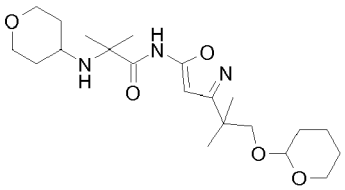
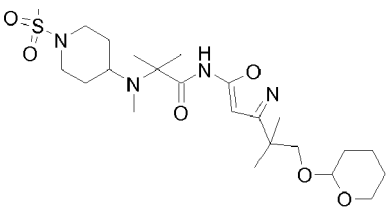
[0072] For intermediate XII and X: the reaction mixture is filtered through celite and washed with DCM. The solvent is removed under reduced pressure and the product purified by column chromatography (silica, eluent; heptanes, 0 - 50% ethyl acetatec)

[0073] According to the above procedure the following intermediates are synthesised:

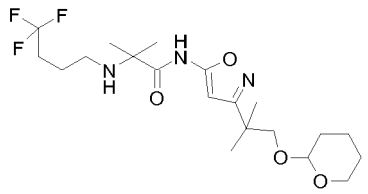
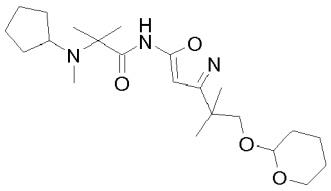
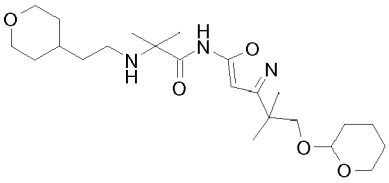
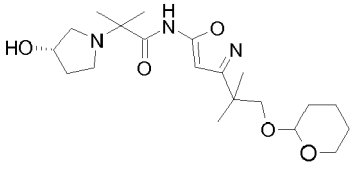
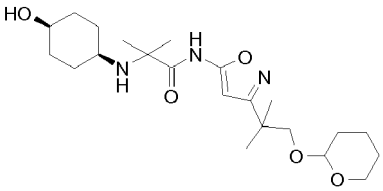
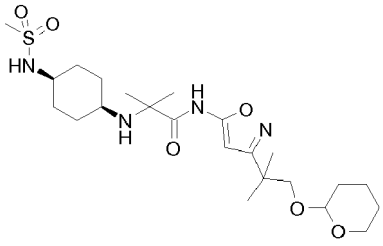
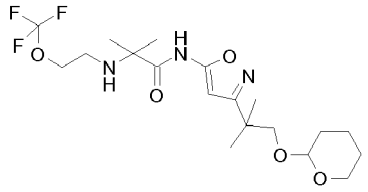
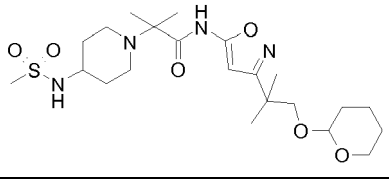
Table 2:

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
III (compound **5**)		41	LC Method b: 1.51	424

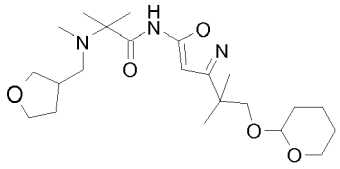
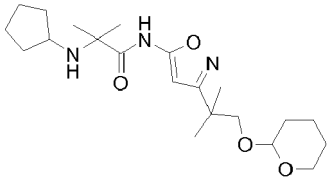
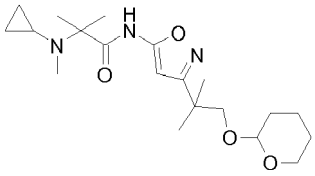
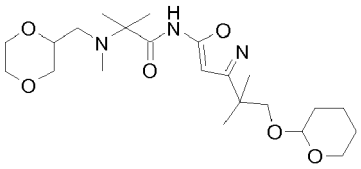
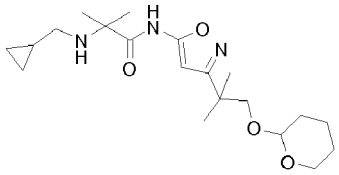
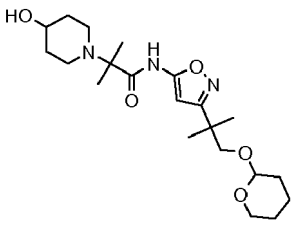
(continued)

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
IV		68	LC Method b: 1.46	394
V		51	LC Method b: 2.11	423
VI		27	not available / see Footnote a	438
VII		51	not available / see Footnote b	382
VIII		66	not available / see Footnote c	487
IX		27	LC Method a: 2.89	424
X		27	LC Method b: 2.05	424
XI		34	LC Method a: 2.74	410
XII		31	LC Method b: 1.48	501

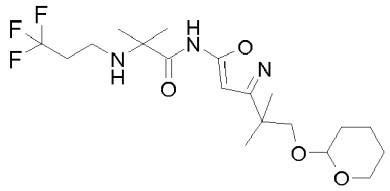
(continued)

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
XIII		n.d.#	LC Method b: 1.50	436
XIV		28	LC Method b: 1.54	408
XV		97	LC Method b: 1.51	438
XVI		n.d.#	LC Method b: 1.34	396
XVII		n.d.#	LC Method b: 1.69	424
XVIII		n.d.#	LC Method b: 1.45	499 [M-H]
XIX		n.d.#	LC Method b: 1.71	436 [M-H]
XX		n.d.#	LC Method b: 1.43	487

(continued)

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
XXI		55	LC Method b: 1.48	424
XXII		56	LC Method b: 1.33	394
XXIII		78	LC Method b: 1.70	380
XXIV		32	LC Method b: 1.99	438 [M-H]
XXV		22	LC Method b: 1.29	380
XXVI		n.d.#	LC Method b: 1.49	410

(continued)

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
XXVII		34	LC Method b: 1.64	420 [M-H]

a) n.d.# intermediate is carried through to the next step without further purificationa) Intermediate VI: ^{1}H NMR (400 MHz, chloroform-d) δ ppm 1.26 (6H, s), 1.34 (3H, s), 1.37 (3H, s), 1.47-1.83 (11H, m), 2.18 (2H, d, 7.2 Hz), 2.22 (3H, s), 3.36-3.50 (3H, m), 3.77-3.82 (3H, m), 3.99 (2H, m), 4.57 (1H, m), 6.32 & 6.38 (1H, 2s), 9.4-9.8 (1H, br)
b) Intermediate VII: ^{1}H NMR (400 MHz, chloroform-d) δ ppm 1.07 (6H, d, J=6.4 Hz), 1.32-1.37 (12H, m), 1.46-1.84 (6H, m), 2.19 (3H, s), 2.98 (1H, q), 3.37 (1H, d, J=9.6 Hz), 3.45-3.50 (1H, m), 3.76-3.81 (2H, m), 4.57 (1H, t, J=6.8 Hz), 6.32 (1H, s), 10.10 (1H, br)
c) Intermediate VIII: ^{1}H NMR (400 MHz, chloroform-d) δppm 1.25 (12H, s), 1.31-1.76 (10H, m), 2.70 (2H, t, 11.2 Hz), 2.80 (3H, s), 3.31-3.42 (6H, m), 3.62-3.66 (2H, m), 4.53 (1H, s), 6.25 (1H, s), 6.80 (1H, br)

Step 3: Synthesis of example 3

[0074] To a solution of compound 5 (806 mg, 1.9 mmol) in DCM/ethanol (1/1, 16 mL) is added polymer-supported tosic acid (MP-TsOH (65), loading 3.3 mmol/g, 1.74 g). The mixture is shaken on an orbital-shaker at room temperature for 18 h. The resin is isolated by filtration and washed with DCM and methanol. The product is then released form the resin with 7M solution of ammonia in methanol. The resin is further rinsed with methanol and DCM. Concentration of the basic filtrate gives a clear oil which is triturated with diethyl ether/heptanes to afford 549 mg of example 3 as a white solid. Yield 85%, LC-MS (LC Method a): retention time: 2.17 min m/z 410 [M+H];, mp 129-131 °C.

[0075] Compounds listed in Table IV under method C are made following this procedure, with the following modification for examples 7-9, and 20: Pyridinium p-toluenesulfonate (1.2 equ) is used instead of MP-TsOH and the reaction is performed under refluxing conditions (4 h) in EtOH instead of DCM/ethanol.

[0076] Example 86-87 are separated by chiral preparative LC.

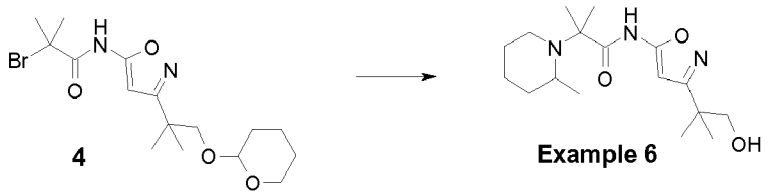
[0077] Example 4 and 5 are converted into the oxalate salt by stirring in the presence of oxalic acid (1 equ) in ethanol at 50 °C, followed by concentration under reduced pressure.

[0078] Examples 42, 43, 45, 47, 48, 49, 51, 53, 56, 57, 60, 63, 64, 68, 86, 87 are converted converted into the hydrochloride salt by stirring in the presence of 1M HCl solution in diethyl ether (2 eq) at room temperature, followed by concentration under reduced pressure.

Method D

Synthesis of Example 6

[0079]



[0080] A solution of 2-methylpiperidine (40 mg, 0.33 mmol), Cs_2CO_3 (218 mg, 0.66 mmol) and compound **4** (130 mg, 0.33 mmol) in THF (10 mL) is heated to 55 °C for 3 h in a pressure tube. After cooling to room temperature, the reaction mixture is diluted with ethyl acetate (40 mL) and washed with brine (2 x 15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: heptanes, 10% ethyl acetate) and then using a Flash SCX-2 cartridge (Isolute®) (eluent: DCM, methanol then 5% NH_3/MeOH) which removes the

tetrahydropyranyl protecting group. Final purification using silica, eluent: heptanes, 10% ethyl acetate) yield 23 mg of example 6. Yield 22%. LC-MS (LC Method a): retention time: 2.35 min, m/z 324 [M+H]

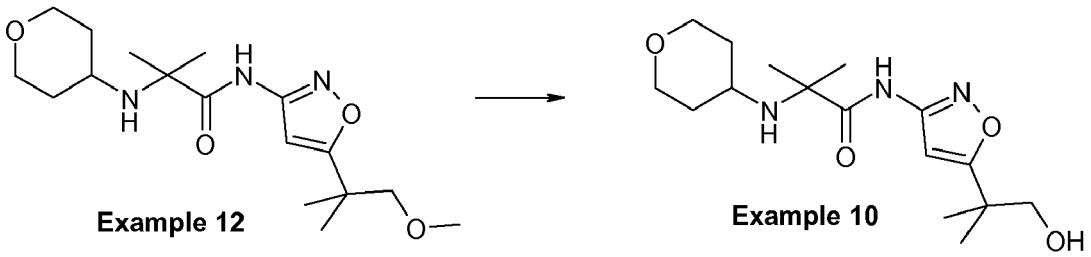
[0081] A portion of example 6 is converted into its hydrochloride salt by stirring in the presence of 1M HCl solution in diethyl ether (2 equ.) at room temperature, followed by concentration under reduced pressure.

[0082] Compounds listed in Table IV under method D are made following this procedure

Method E

Synthesis of Example 10

[0083]



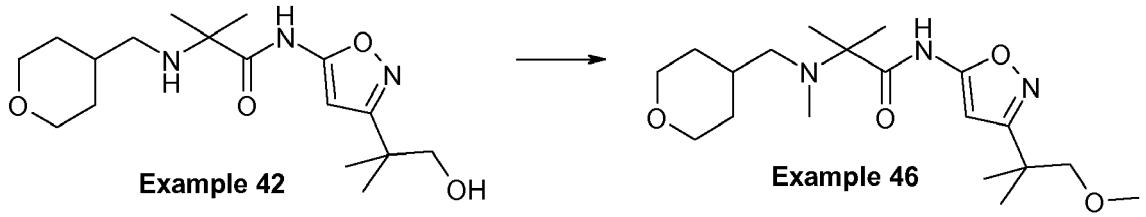
[0084] Example 12 (80 mg, 0.24 mmol, prepared according to Method A) and 600 mg (2.35 mmol) of aluminium tribromide are dissolved in ethanethiol (4 mL, CAUTION: stench) and stirred at room temperature for 3 h. The reaction is quenched by addition of water (8 mL) and acidified by careful addition of 1 M aqueous HCl solution to pH 4-5. The reaction mixture is extracted with ethyl acetate (3 x 10 mL) and the combined organic layers are washed with brine, dried over Na_2SO_4 and filtered. The filtrate is concentrated under reduced pressure and the residue purified by column chromatography (silica, eluent: DCM, 50% ethyl acetate) to afford 50 mg of example 10. Yield 65%, LC-MS (LC Method a): retention time: 2.14 min, m/z 326 [M+H]

[0085] Compounds listed in Table IV under method E are made following this procedure

Method F

Synthesis of Example 46

[0086]



[0087] To a solution of example 42 (0.34g, 1.01 mmol) and NaH (0.12 g, 3.04 mmol, 60% dispersion in mineral oil,) in THF (6 mL) is added methyl iodide (95 μL, 1.52 mmol). The reaction mixture is stirred at room temperature for 18 h and filtered through celite. The crude product is purified by preparative HPLC (neutral method) to yield 53 mg of example 46 as a colourless oil. Yield: 17%, LC-MS (LC Method a): retention time: 2.60 min, m/z 368 [M+H].

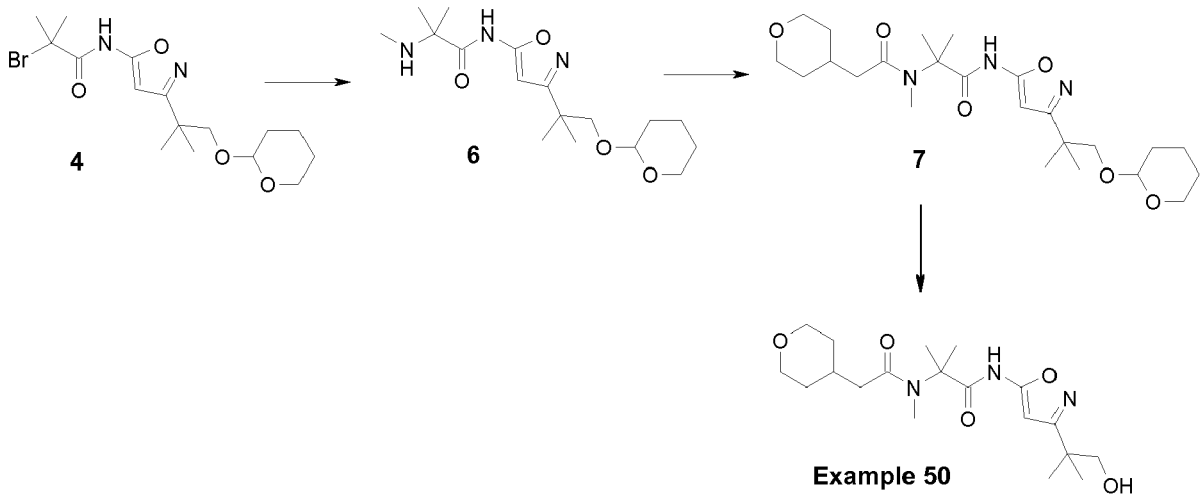
example 46 is converted to the hydrochloride salt by stirring in the presence of 2M solution of hydrogen chloride in diethyl ether (1 mL) at room temperature, followed by concentration under reduced pressure.

[0088] Compounds listed in Table IV under method F are made following this procedure

Method G

Synthesis of Example 50

[0089]



Step 1: Synthesis of compound 6

[0090] A solution of methylamine (2.89 mL, 23.1 mmol), Cs_2CO_3 (0.75 g, 2.3 mmol) and compound **4** (0.45 g, 1.2 mmol) in THF (10 mL) is heated to 65 °C in a sealed tube for 3 h. The reaction mixture is cooled and diluted with ethyl acetate (20 mL). The mixture is washed with brine (8 mL). The organic layer is dried ($MgSO_4$), filtered and the filtrate is concentrated under reduced pressure. The crude product is purified by column chromatography (silica, eluent: heptanes, 0-50% ethyl acetate) to yield 0.29 g of compound 6. Yield: 74%; LC-MS (LC Method b): retention time: 1.24 min, m/z 340 [M+H].

Step 2: Synthesis of compound 7

[0091] To a solution of compound 6 (0.2 g, 0.59 mmol) and N,N-diisopropylethylamine (0.2 mL, 1.18 mmol) in THF (8 mL) is added (tetrahydro-pyran-4-yl)-acetyl chloride (0.11 g, 0.59 mmol). The reaction is heated to 60 °C for 18 h and the solvent is removed under reduced pressure. The residue is dissolved in ethyl acetate (20 mL) and washed with water (2 x 5 mL) and brine (2 x 5 mL). The organic layer is dried ($MgSO_4$), filtered and the filtrate is concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent: heptanes, 0-50% ethyl acetate) to yield 0.25 g of compound 7; yield: 94%, LC-MS (LC Method b): retention time: 1.90 min, m/z 464 [M-H].

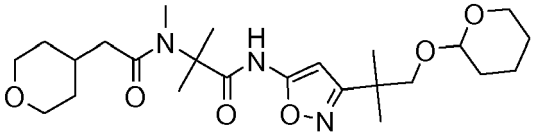
[0092] According to the above method the following intermediates are synthesised with the following modifications to be noted:

For intermediate XXX and XXXIII, the corresponding acid is converted into its acidchloride by treatment with oxalylchloride (4 equ.) and DMF (cat) in DCM at room temperature for 4 h. The reaction mixture is concentrated under reduced pressure and the crude acid chloride is used in the above procedure without further purification.

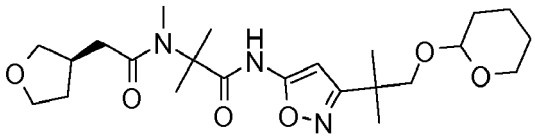
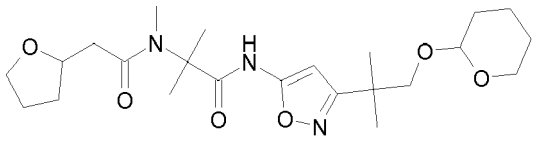
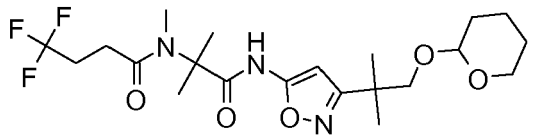
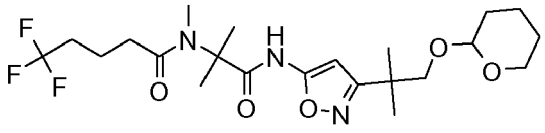
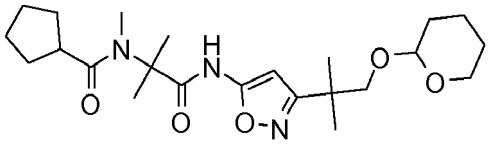
[0093] Intermediates XXXI and XXXII are synthesised using standard amide coupling conditions: 1 equ of compound 6 is coupled with the corresponding acid (1 equ) using EDC.HCl (3 equ) and DMAP (1 equ) in acetonitrile. The reaction mixture is stirred at room temperature for 18 h and the concentrated under reduced pressure. The residue is purified by column chromatography (silica, eluent:n-heptanes, 30% ethyl actetate) to afford the desired intermediate.

[0094] According to the above procedure the following intermediates are synthesised:

Table 3:

Intermediate No.	**Structure**	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
XXVIII (compound 7)		94	LC Method b: 1.90	464 [M-H]

(continued)

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
XXIX		22	LC Method b: 1.83	474 [M+Na]
XXX		86	LC Method b: 1.89	474 [M+Na]
XXXI		69	LC Method b: 2.08	486 [M+Na]
XXXII		82	LC Method b: 2.11	500 [M+Na]
XXXIII		35	LC Method b: 2.10	458 [M+Na]

Step 3: Synthesis of example 50

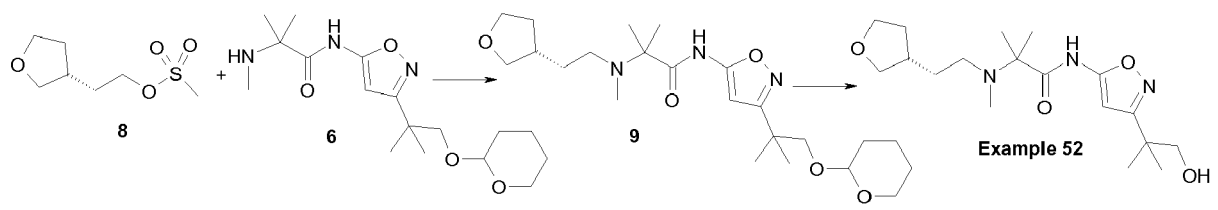
[0095] Compound 7 is deprotected by shaking in the presence of polymer-supported tosic acid (MP-TsOH (65), loading 3.3 mmol/g, 0.6 g) on an orbital shaker for 18 h. The resin is removed by filtration and washed with DCM. The product is released from the resin by treatment with 7M ammonia in methanol and the filtrate is concentrated under reduced pressure and the residue is purified by preparative HPLC (neutral method) to afford 40 mg of example 50. Yield 18%, LC-MS (LC Method a): retention time: 3.06 min, m/z 382 [M+H].

[0096] Compounds listed in Table IV under method G are made following this procedure

Method H

Synthesis of Example 52

[0097]



Step 1: Synthesis of compound 9

[0098] To a solution of compound 6 (0.2 g, 0.59 mmol, prepared according to Method G, step 1) and Cs_2CO_3 (0.38

g, 1.18 mmol) in THF (3 mL) is added compound **8** (115 mg, 1.0 mmol, prepared as described in Gosh, A.K. et al. J. Med. Chem. 1993, 36, 2300-2310). The reaction is heated to 65 °C for 3 h in a sealed tube and diluted in ethyl acetate (12 mL). The organic layer is washed with brine (8 mL) and dried ($MgSO_4$). The solvent is removed under reduced pressure and purified by column chromatography (silica, eluent: heptanes, 0-50% ethyl acetate) to afford 0.2 g of compound 9. Yield: 12%; LC-MS (LC Method b): retention time: 1.37 min, m/z 438 [M+H].

Step 2: Synthesis of Example 52

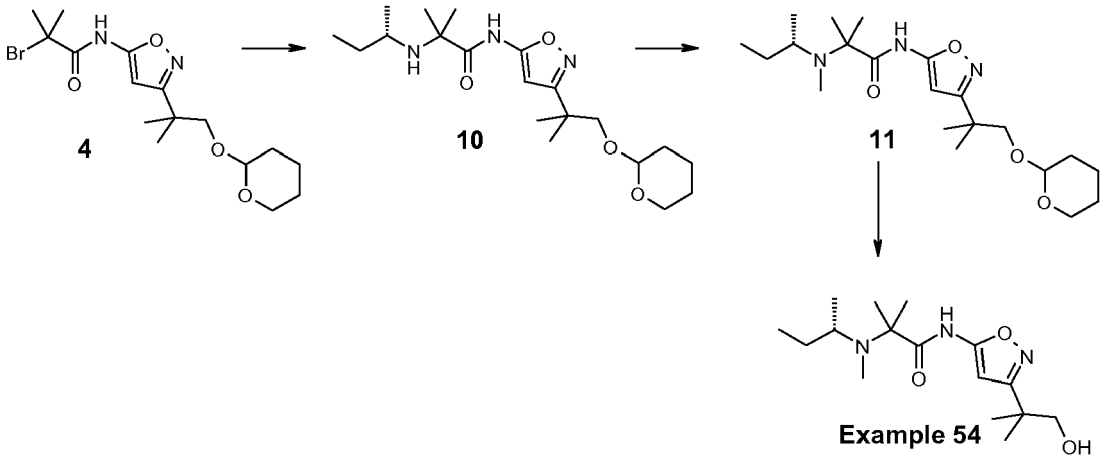
[0099] To a solution of compound **9** in DCM/methanol (1/1, 4 mL) is added polymer-supported tosic acid (MP-TsOH (65), loading 3.3 mmol/g, 0.28 g) and the reaction mixture is shaken on an orbital shaker for 18 h. The resin is removed by filtration and washed with DCM. The product is released from the resin by treatment with 7M ammonia solution in methanol and the resin is further washed with methanol and DCM. The filtrate is concentrated under reduced pressure. The residue is purified by preparative LC (neutral method) to afford 69 mg of example 52 as a clear oil, yield 36%, LC-MS (LC Method a): retention time: 2.19 min, m/z 354 [M+H], which is converted in its hydrochloride salt by treatment with 2M HCl in diethyl ether (0.12 mL) and concentration under reduced pressure. The crude material is recrystallised from ethyl acetate/heptanes to afford the hydrochloride salt of example 52 as a white crystalline solid.

[0100] Compounds listed in Table IV under method H are made following this procedure

Method I

Synthesis of Example 54

[0101]



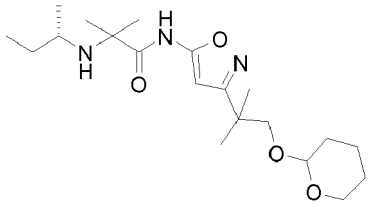
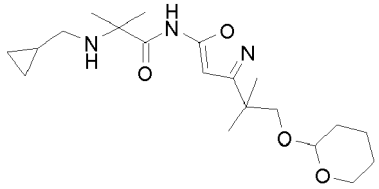
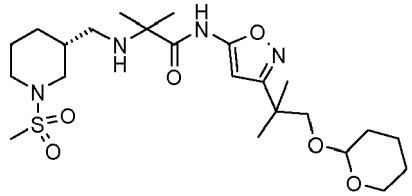
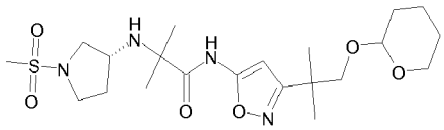
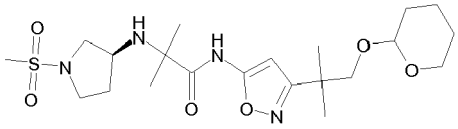
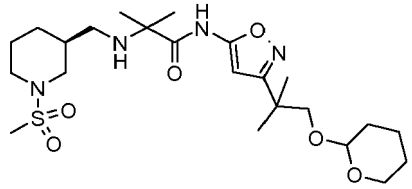
Step 1: Synthesis of compound 10

[0102] A solution of (S)-sec-butylamine (0.3 g, 4.1 mmol), Cs_2CO_3 (2.67 g, 8.2 mmol) and compound **4** (1.59 g, 4.1 mmol) in THF (10 mL) is stirred at room temperature for 18 h. The reaction mixture is heated to 50 °C for 1 h and the reaction is filtered through celite. The solids are washed with DCM and ethyl acetate and the filtrate is concentrated under reduced pressure to afford a yellow oil. This residue is purified by column chromatography (silica, eluent: heptanes, 50% ethyl acetate) to yield 0.65 g of compound **10.** Yield: 42%, LC-MS (LC Method b): retention time: 1.38 min, m/z 382 [M+H].

[0103] The following intermediates are made according to the above procedure.

[0104] According to the above procedure the following intermediates are synthesised:

Table 4:

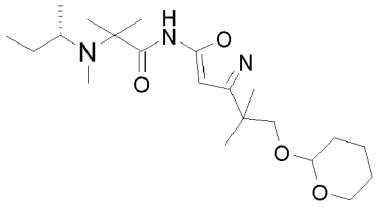
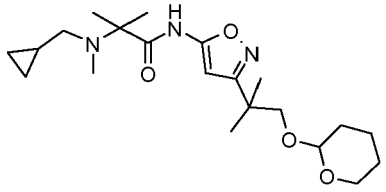
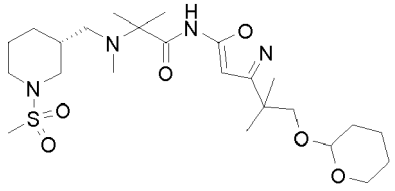
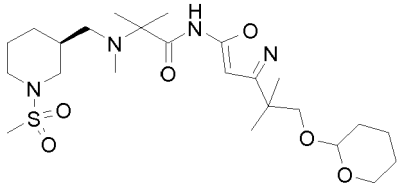
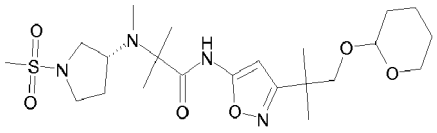
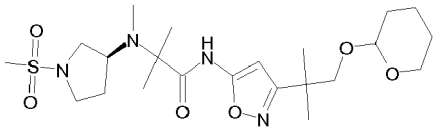
Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
XXXIV (compound 10)		25	LC Method b: 1.38	382
XXXV		22	LC Method b: 1.29	380
XXXVI		37	LC Method b:1.47	501
XXXVII		48	LC Method b:1.50	471 [M-H]
XXXVIII		50	LC Method b:1.50	471 [M-H]
XXXIX		66	LC Method b: 1.43	501

Step 2: Synthesis of compound 11

[0105] To a solution of the compound **10** (392 mg, 1.02 mmol) in THF (3 mL) is added sodium hydride (41 mg, 1.02 mmol, 60% dispersion in mineral oil) and methyl iodide (64 μl, 1.02 mmol). The reaction mixture is heated to 70 °C for 1 h in a microwave. The reaction mixture is concentrated under reduced pressure and the residue is dissolved in methanol and filtered. The filtrate is concentrated under reduced pressure and the crude material is purified by preparative HPLC (neutral method) to afford 137 mg of compound **11** as a clear oil. Yield: 34%, LC-MS (LC Method b): retention time: 1.25 min, m/z 396 [M+H].

[0106] The following intermediates are made according to the above procedure.

Table 5:

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
XXXX (compound **11)**		33	LC Method b: 1.25	396
XLI		59	LC Method b: 1.22	394
XLII		60	LC Method b: 1.63	515
XLIII		52	LC Method b: 1.63	515
XLIV		36	LC Method b:1.94	485 [M-H]
XLV		49	LC Method b:1.94	485 [M-H]

Step 3: Synthesis of Example 54

[0107] To a solution of compound **11** (137 mg, 0.34 mmol) in DCM/methanol (1/1, 10 mL) is added polymer-supported tosic acid (MP-TsOH (65), loading 3.3 mmol/g, 0.31 g). The mixture is shaken on an orbital-shaker at room temperature for 18 h. The resin is isolated by filtration and washed with DCM. The product is then released from the resin with 2M solution of ammonia in methanol. Concentration of the basic filtrate affords 88 mg of example 54. Yield: 63%, LC-MS (LC Method a): retention time: 2.35 min, m/z 312 [M+H].

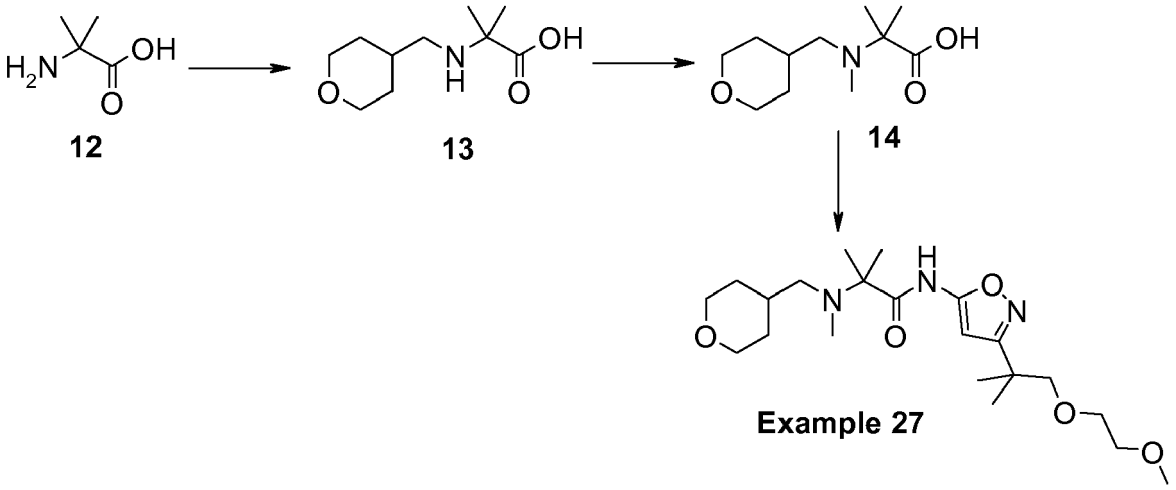
[0108] Compounds listed in Table IV under method I are made following this procedure with the following modifications to be noted:

Example 54, 55, 84, 85 are converted into the hydrochloride salt by stirring in the presence of hydrogen chloride in diethyl ether (2M, 1 mL) at room temperature, followed by concentration under reduced pressure.

Method J

Synthesis of Example 27

[0109]



Step 1: Synthesis of compound 13

[0110] A high pressure vessel on the HEL 100 system containing compound 12 (2.5 g; 24.244 mmol) and tetrahydropyran-4-carbaldehyde (5.05 mL; 48.487 mmol) is added palladium hydroxide, 20% on carbon, wet (3.405 g; 10 mol%; 2.424 mmol) and 50 mL of ethanol. The reaction is subjected to 400 psi H_2 at 50 °C for 40 h. After this time, the reaction is cooled to room temperature and filtered through Celite®. The Celite® is rinsed with methanol and water. The combined filtrates are concentrated and slurried in dichloromethane, then filtered to afford compound 13 as a white solid (3.95g; 81%), LC-MS (LC Method h): retention time 0.32 min, m/z 202 $[M+H]^+$

Step 2: Synthesis of compound 14

[0111] A high pressure vessel on the HEL 100 system containing compound **13** (1g; 4.969mmol) and formaldehyde, 37% in water (0.74mL; 9.937mmol) is added palladium hydroxide, 20% on carbon, wet (0.698g; 10mol%; 0.497mmol) and 30mL of ethanol. The reaction is subjected to 400 psi H_2 at 100 °C for 27.5 h. After this time, the reaction is cooled to room temperature and filtered through Celite®. The Celite® is rinsed with methanol and water. The combined filtrates are concentrated to afford compound **14** as a colorless oil (1.364g; quantitative), LC-MS (LC Method h): retention time 0.32 min, m/z 216 $[M+H]^+$

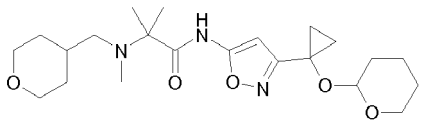
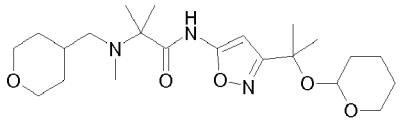
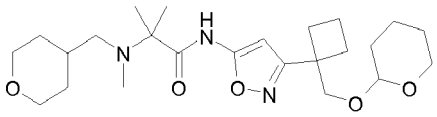
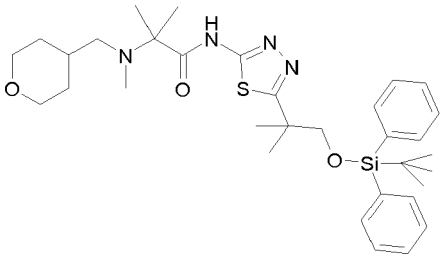
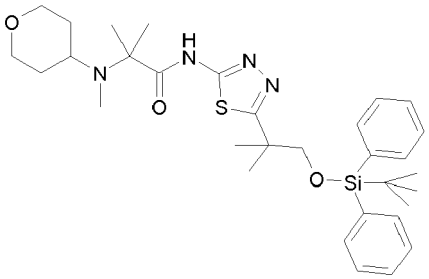
Step 3: Synthesis of Example 27

[0112] To a vial containing compound **14** (0.2g; 0.929 mmol) is added *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.530g; 1.394 mmol) and N,N-diisopropylethylamine (0.579mL; 3.252mmol). The solution is stirred at room temperature for 30 minutes. To a vial containing 3-[2-(2-methoxy-ethoxy)-1,1-dimethyl-ethyl]-isoxazol-5-yl-amine (0.199g; 0.929mmol) is added N,N-dimethylformamide (2mL) and sodium hydride (0.093g; 2.323mmol) at 0 °C. To this solution is added the activated ester. Once addition is complete, the cold bath is removed and the reaction warmed to room temperature and stirred for 1h. The reaction is quenched with methanol/water and concentrated under reduced pressure. Purification is done by reverse phase HPLC to afford example 27 (0.107g; 28%), LC-MS (LC Method c): retention time 0.97 min, m/z 412 $[M+H]^+$.

[0113] Compounds listed in Table IV under method J are made following this procedure with the following modifications to be noted: for example 26, 28, and 32 TBTU (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate) is used as the coupling reagent instead of HATU as described in step 3.

[0114] Compounds listed in Table IV under method J are made following this procedure
The following intermediates are made according to the above procedure.

Table 6:

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
XLVI		crude	LC Method d: 1.08	422
XLVII		crude	LC Method d: 1.08	424
XLVIII		31	LC Method c: 1.08	450
XLIX		23	LC Method c:, 1.70	609
L		23	LC Method c:, 1.80	595

Method J1

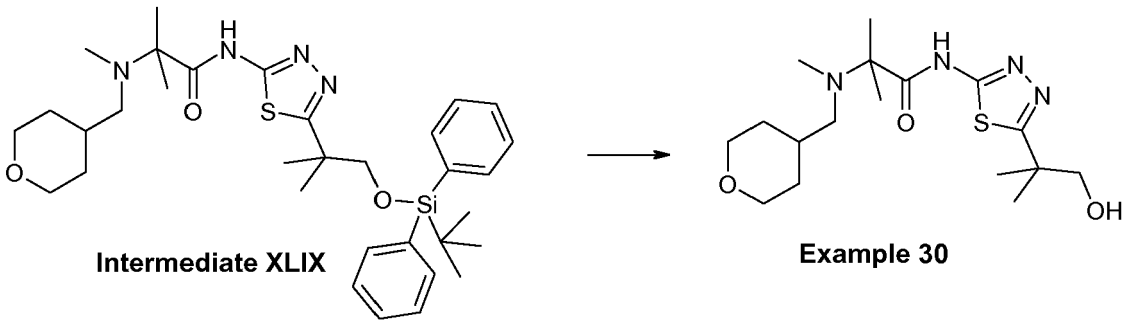
[0115] Same as Method C step 3.

[0116] Compounds listed in Table IV under Method J1 are made following this procedure.

Method J2

Synthesis of Example 30

[0117]



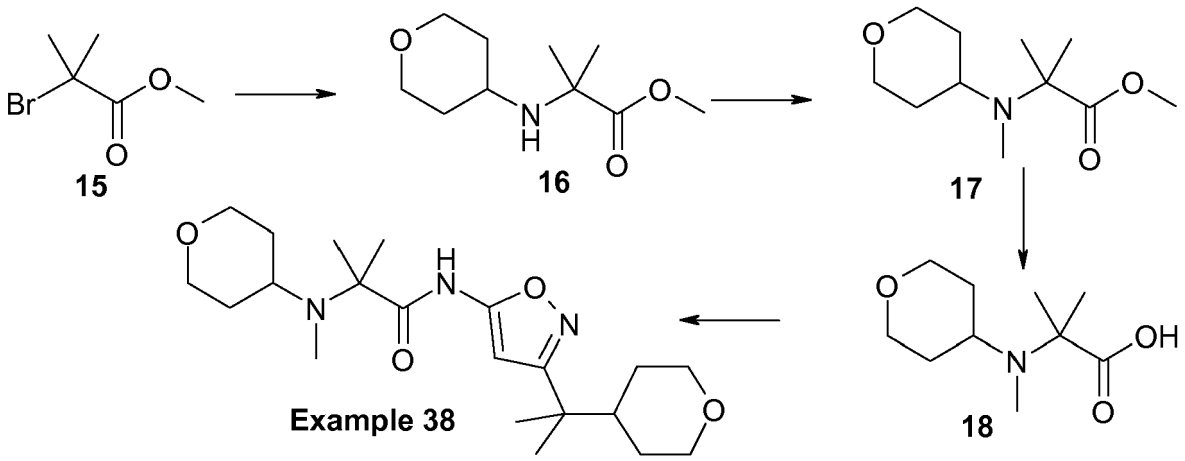
[0118] Intermediate XLIX (0.127 g; 0.209 mmol) is diluted with 3 mL methanol and HF pyridine complex (0.130 ml; 1.045 mmol; 70%) is added. The reaction is heated at 45°C in a sealed tube for 7 days adding aliquots of HF pyridine complex on a daily basis. Concentrated and purified by prepartive HPLC. Pooled product fractions and concentrated. Diluted in methanol and passed through a cartridge containing MP-Carbonate resin to neutralize molecule from trifluoroacetic acid contained in HPLC mobile phase to afford example 30 (0.024 g; 31.1 %); LC-MS (LC method c): retention time 0.40 min, m/z 371[M+H$^+$]

[0119] Compounds listed in Table IV under Method J2 are made following this procedure.

Method K:

Synthesis of Example 38

[0120]

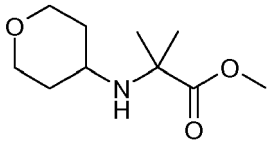
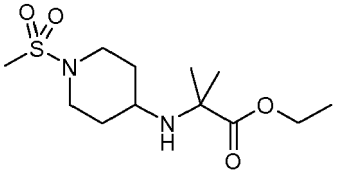


Step 1: Synthesis of compound 16

[0121] Compound 15 (6.4mL, 49.4mmol) is dissolved in 100mL of acetonitrile under nitrogen and potassium iodide (739mg, 4.5mmol) is added followed by the addition of potassium carbonate (13.7g, 98.9mmol) and 4-aminotetrahydropyran (5g, 49.4mmol). The reaction mixture is heated in 90°C oil bath for 16 hours, After this time, the reaction mixture is cooled to room temperature and methyl 2-bromoisobutyrate (1.6mL, 12.4mmol) and potassium iodode (184.5mg, 1.11mmol) are added and the reaction mixture is heated in 90°C oil bath for 18 hours. After this time, the reaction mixture is cooled to room temperature and filtered through a glass funnel and the solid is washed with acetonitrile. The filtrate is concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel using ethyl acetate/heptane provides compound **16** (36%), LC-MS (LC method d): retention time: 0.27 min, m/z 202 [M+H$^+$].

[0122] The following intermediates aree made following the above procedure:

Table 7:

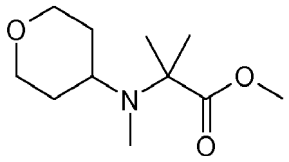
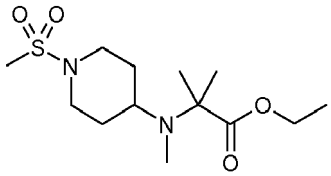
Intermde diate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
LI (compou nd **16)**		36	LC Method d: 0.27	202
LII		31	LC Method d: 0.60	293
Notes: starting material for intermediate I is ethyl 2-bromoisobutyrate.				

Step 2: Synthesis of compound 17

[0123] Methyl iodide (2.5mL, 39.9mmol) is added dropwise to a mixture of compound 16 (4.38g, 17.7mmol) and potassium carbonate (10.94g, 79.1mmol) in 74mL of DMF. The reaction mixture is stirred at room temperature for 18 hours. After this time, methyl iodide (1mL, 16mmol) is added and the reaction mixture is stirred at room temperature for 65 hours. After this time, the reaction mixture is filtered and the solid is washed with ethyl acetate. The filtrate is concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel using ethyl acetate/heptane provides compound 17 (78%), LC-MS (Method d): retention time: 0.27 min, m/z 216 [M+H$^+$].

[0124] The following intermediates are made following the above procedure:

Table 8:

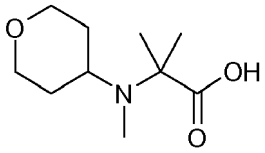
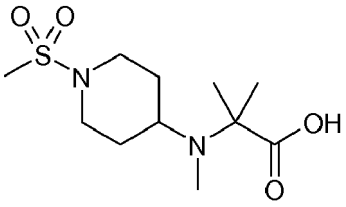
Intermedi ate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
LIII (compou n **17**)		78	LC Method d: 0.27	216
LIV		88	LC Method d: 1.27	307

Step 3: Synthesis of compound 18

[0125] Compound **17** (3.24g, 13.8mmol) is dissolved in 14mL of methanol in a pressure tube and sodium hydroxide aqueous solution (4N, 13.8mL, 55.3mmol) is added and the reaction mixture is heated in 80°C oil bath for 3 hours. After this time, the reaction mixture is concentrated under reduced pressure and the residue is neutralized to pH ~ 7 by adding 1N HCl aqueous solution. The resulting solution is diluted with acetonitrile and dried in lyophilizer for 18 hours. After this time, the solid is suspended in acetone and filtered. The filtrate is concentrated under reduced pressure to afford compound **18** (100%), LC-MS (LC Method d): retention time: 0.29 min, m/z 202 [M+H$^+$].

[0126] The following intermediates are made following the above procedure:

Table 9:

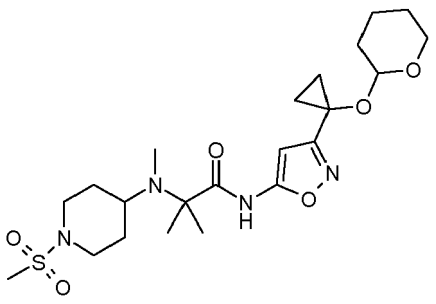
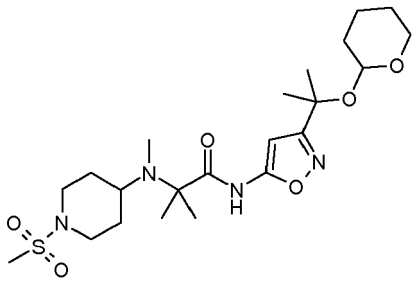
Intermedi ate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
LV compoun **18)**		100	LC Method d: 0.29	202
LVI		33	LC Method d: 0.32	279

Step 4: Synthesis of Example 38

[0127] To a vial containing compound **18** (142mg, 0.707mmol) in 1mL of DMF is added O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (272mg, 0.848mmol) and diisopropylethylamine (0.27mL, 1.55mmol). The mixture is stirred at room temperature for 1 hour. To a vial contaning compound 25 (149mg, 0.707mmol) in 1.2mL of DMF is added sodium hydride in mineral oil (60%, 62mg, 1.55mmol). The mixture is stirred at room temperature for 15 minutes. To this solution is added dropwise the activated ester. The reaction mixture is stirred at room temperature for 1.5 hours. After this time, the reaction mixture is concentrated under reduce pressure to remove the solvent. The residue is quenched with saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate twice. The organcis are combined and washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel using methanol/methylene chloride provides example 38 (17%), LC-MS (LC method d): retention time 1.03 min, m/z 394 [$M+H^+$].

[0128] Compounds listed in Table IV under Method K are made following this procedure. Also, the following intermediates are made following this procedure.

Table 10:

Intermedi ate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
LVII		45	LC Method f: 1.28	485
LVIII		quantitative	LC Method c:, 1.12	487

Method K1

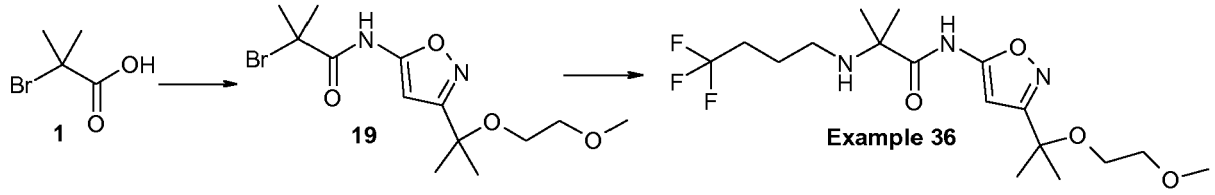
[0129] Same as Method C step 3.

[0130] Compounds listed in Table IV under Method K1 are made following this procedure.

Method L

Synthesis of Example 36

[0131]

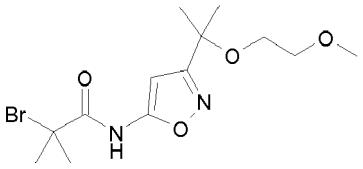
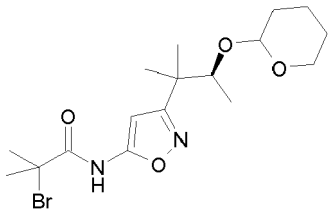


Step 1: Synthesis of compound 19

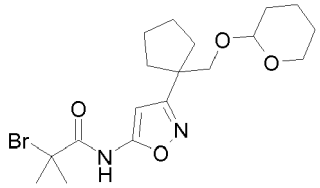
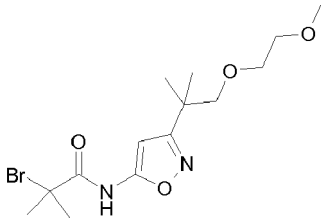
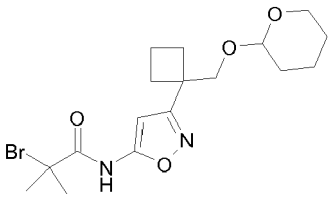
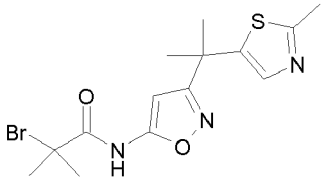
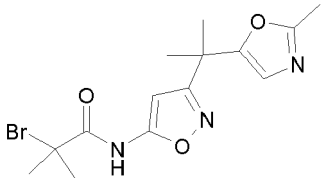
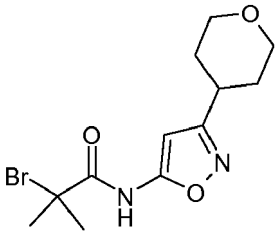
[0132] To a pressure vessel containing compound **1** (1.25g, 7.49mmol) under nitrogen is added thionyl chloride (2.5mL, 34.5mmol) and catalytic amount of DMF, The pressure vessel is sealed and heated to 70°C where it is maintained for 2 hours. After this time, the reaction mixture is cooled to room temperature and diluted with dichloromethane and the acid chloride solution is concentrated in vacuo until ~ 1mL left and this process is repeated twice. The crude acid chloride is used without further purification. The crude acid chloride is diluted with 2mL of tolune and added to the vial containing 3-[1-(2-Methoxy-ethoxy)-1-methyl-ethyl]-isoxazol-5-ylamine (1g, 5.0mmol) and N,N-diisopropylethylamine (4.35mL, 24.98mmol) in 10mL of toluene and the reaction mixture is heated at 55°C for 18 hours. After this time, the reaction mixture is quenched with saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel using ethyl acetate/heptane provides compound **19** (52%), m/z 350 [M+H$^+$]

[0133] Compounds listed in intermediate table below are made following this procedure with the following modifications to be noted: for LXII reaction with thionyl chloride is heated at 80°C, for LXIV-LXV reaction with thionyl chloride is heated at 60 °C.

Table 11:

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M/M+2H]
LIX(compoun **19)**		52	LC Method d:1.30	349/351
LX		64	LC Method d:1.49	319/321 [M-THP/M-THP+2H]

(continued)

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M/M+2H]
LXI		58	LC Method d:1.52	331/333 [M-THP/M-THP+2H]
LXII		13	LC Method c: 1.28	363/365
LXIII		38	LC Method c: 1.49	317/319 [M-THP/M-THP+2H]
LXIV		31	LC Method c: 1.29	372/374
LXV		32	LC Method c: 1.23	356/358
LXVI		90	LC Method d:1.25	317/319 [M/ M+2H]

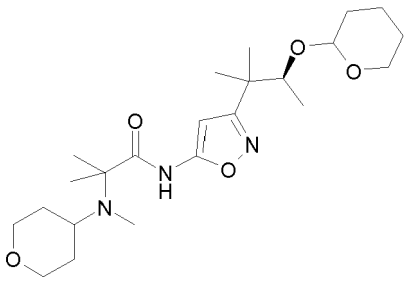
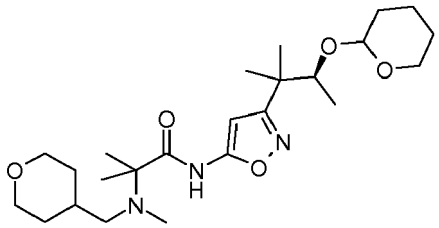
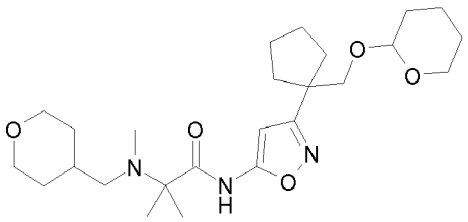
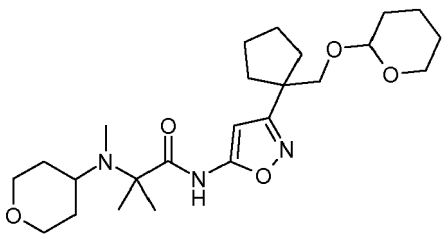
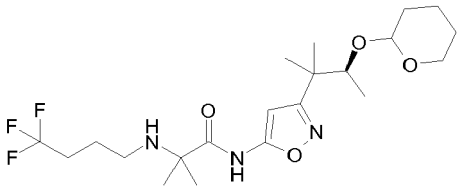
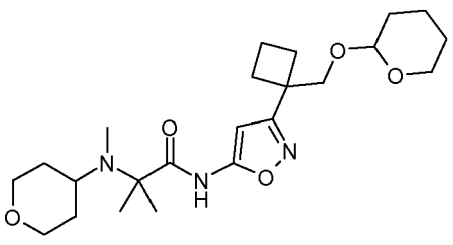
Step 2: Synthesis of Example 36

[0134] Sodium hydride in mineral oil (60%, 61.8mg, 1.55mmol) is suspended in 2mL of THF and the solution of 4,4,4-Trifluoro-butylamine (81.9mg, 0.64mmol) in 1mL of THF is added and the mixture is stirred at room temperature for 5 minutes under nitrogen before dropwise adding the solution of compound **19** (180mg, 0.52mmol) in 1.5mL of THF. The reaction mixture is stirred at room temperature for 18 hours. After this time, the reaction mixture is quenched with saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel using ethyl acetate/heptane provides example 36 (47%), LC-MS (LC Method d): retention time 1.05 min, m/z 396 [$M+H^+$].

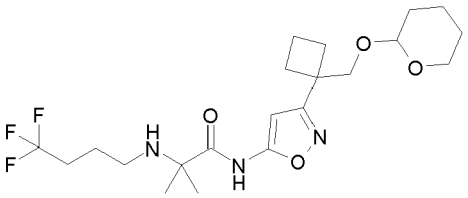
[0135] Compounds listed in Table IV under Method L are made following this procedure, with the exception of example 14, 31, and 76 for which the last step is run according to Method B Step 2, and the crude is purified by prep HPLC or silica gel chromatography. Further for example 15 in Table IV NaH (4 equivalents) in mineral oil is used.

[0136] Also, the following intermediates are made following this procedure, with the exeption that for intermediates LXVII-LXXI NaH (4 equivalents) in mineral oil is used.

Table 12:

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
LXVII		27	LC Method d:1.15	438
LXVIII		42	LC Method d:1.14	452
LXIX		34	LC Method d:1.17	464
LXX		16	LC Method d:1.16	450
LXXI		65	LC Method d:1.20	450
LXXII		quantitati ve	LC Method d:1.32	436

(continued)

Intermediate No.	Structure	Yield [%]	LC Method and Retention time [min]	m/z [M+H]
LXXIII		61	LC Method c1.14	448

Method L1

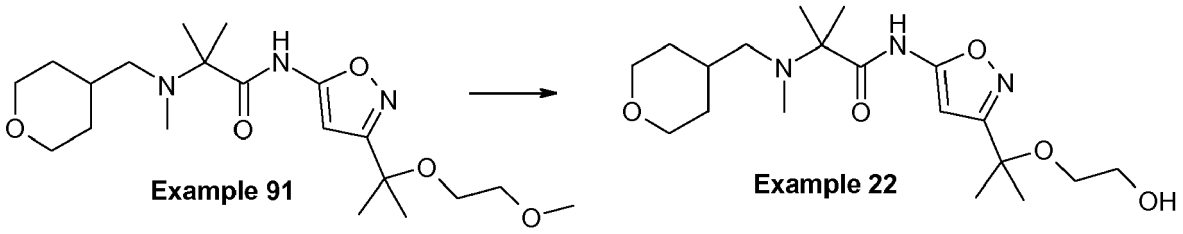
[0137] Same as Method C step 3.

[0138] Compounds listed in Table IV under Method L1 are made following this procedure.

Method M

Synthesis of Example 22

[0139]



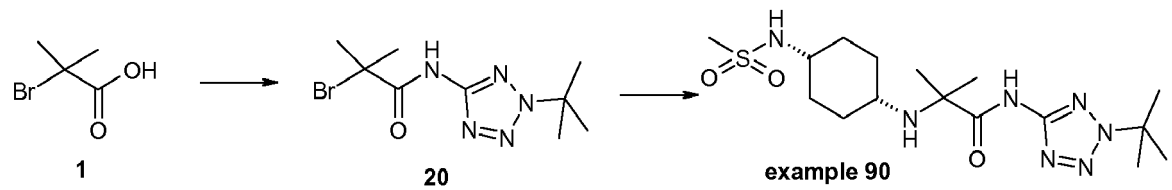
[0140] Aluminium chloride (188mg, 1.4mmol) is added to a cooled (0°C) suspension of example 91 (33mg, 0.083mmol) in ethanethiol (1mL, 13.5mmol). The reaction mixture is stirred at room temperature for 65 hours. Aluminum chloride (100mg, 0.74mmol) is added and the reaction mixture is stirred at room temperature for 24 hours. After this time, the reaction mixture is quenched with 20mL of water and 5 drops of concentrated hydrochloric acid aqueous solution and the mixture is stirred at room temperature for 1 hour. The mixture is extracted with ethyl acetate and the layers are separated. The aquous layer is basicified to pH ~14 by adding 4N sodium hydroxide aqueous solution and the resulting mixture is extracted with ethyl acetate twice. The organics are combined and washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel using methanol/methylene chloride provides example 22 (88%), m/z 384 [$M+H^+$].

[0141] Compounds listed in Table IV under Method M are made following this procedure.

Method N

Synthesis of Example 90

[0142]



Step 1: Synthesis of Compound 20

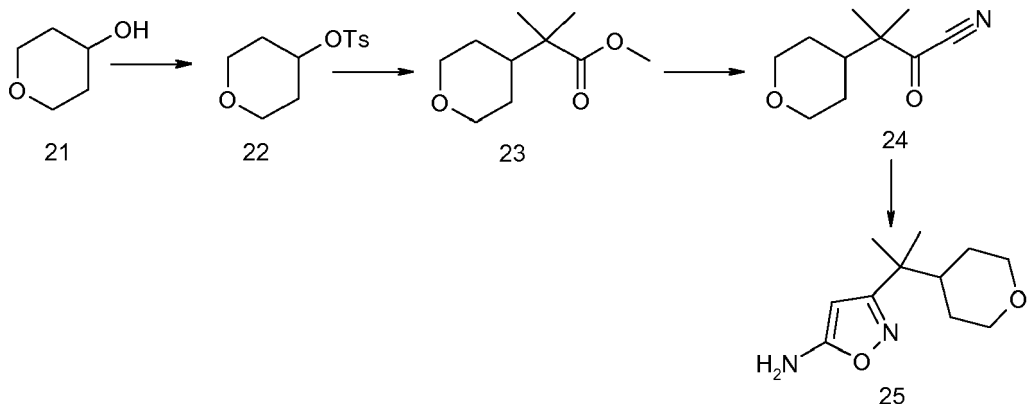
[0143] To a flask containing compound 1 (11.8 g, 71 mmol) in MeCN (500 mL) is added EDC.HCl (37.7 g, 212 mmol) and DMAP (8.6 mg, 71 mmol) at room temperature. 2-tert-butyl-2H-tetrazol-5-ylamine (10 g, 71 mmol) is added and the reaction mixture is stirred at room temperature for 24 h. Water (50 mL) is added and extracted with ethyl acetate (3 x 250 mL). The combined organic layers are dried (Na_2SO_4) and the solvent is concentrated under reduced pressure. The crude material is purified by column chromatography (silica, eluent: heptanes, 0 - 50% ethyl acetate) to afford 9.4 g of compound **20.** Yield: 45%, LC-MS (LC Method b): retention time: 1.71 min, m/z 290/292 [M+H].

Step 2: Synthesis of Example 90

[0144] N-(cis-4-Aminocyclohexyl)methanesulfonamide (0.22 g, 1.14 mmol) and compound 20 (0.32 g, 1.14 mmol) are charged into a pressure tube. The reaction mixture is heated to 150 °C for 20 min until the solids are melted. After cooling to room temperature, the residue is dissolved in ethyl acetate (10 mL) and washed with saturated $NaHCO_3$ solution (10 mL). The aqueous layer is extracted with ethyl acetate (2 x 20 mL) and the combined organic layers are dried over Na_2SO_4 and filtered. The filtrate is concentrated under reduced pressure and the residue is purified by preparative LC (neutral method) followed by column chromatography (silica, eluent: heptanes, 0-60% ethyl acetate) to afford 6 mg of example 90. Yield: 1.3 %, LC-MS (LC Method a): retention time: 2.36 min, m/z 402 [M+H].

Synthesis of compound 25

[0145]



Step1: Synthesis of Compound 22

[0146] Paratoluenesulfonyl chloride (300.0 g, 1.58 mol) is added to a solution of compound 21 (100.0 g, 0.98 mol) in 800.0 mL of pyridine at 0°C. After stirring the reaction mixture at room temperature for 14 hours, it is pored into an ice solution of 6N HCl. Some precipitate is formed that is filtered and triturated with hexanes. After drying under vacuum the crude compound 22 is used without further purification in the next step. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 1.70-1.89 (4H, m), 2.45 (3H, s), 3.44-3.50 (2H, m), 3.86 (2H, p), 4.70 (1H, m), 7.33 (2H, d, 8.4 Hz), 7.79 (2H, d, 8.0 Hz).

Step2: Stynthesis of compound 23

[0147] n-BuLi (1.6M solution in hexane, 122.5 mL) is added slowly to a stirred solution of DIPA in dry THF (150 mL) at -78 °C. After stirring the solution for 1 h at -78 °C, Isobutyric acid methyl ester (10.0g, 98.0 mmol) is added slowly and stirred for 3 h at -78 °C. Compound **22** (25.1g, 98.0 mmol) is dissolved in THF and added to the reaction mixture that is stirred for 1 h at -78 °C and 14 h at room temperature. The reaction mixture is quenched with water and extracted with ethyl acetate. The organic layer is washed with water and brine, dried over *anhy.* Na_2SO_4, filtered and concentrated under vacuum. The crude is purified by silica flash column chromatography (30% Ethyl actetate in heptane), to afford 7.0 g of the compound **23** as a pale yellow oil. Yield: 38%. ^{1}H NMR (400 MHz, chloroform-d) δ ppm 1.13 (6H, s), 1.38-1.45 (4H, m), 1.78-1.85 (1H, m), 3.33-3.40 (2H, m), 3.66 (3H, s), 3.98 (2H, dd, 2.8 Hz).

Step 3: Synthesis of compound 24

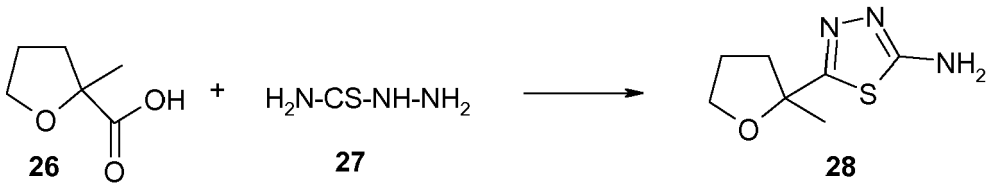
[0148] A solution of compound **23** (6.0g, 32.2mmol) in CH_3CN (2.2mL) is added to a stirred suspension of NaH (2.1g, 48.3mmol) in toluene (60.0mL) at 80 °C and the reaction mixture is further maintained at reflux temperature for 14 h. The reaction mixture is cooled to room temperature; water is added and extracted with EtOAc (3 times). The aqueous layer is acidified with 2N *aq*. HCl solution and extracted with EtOAc. The combined EtOAc layers are washed with brine, dried over *anhy.* Na_2SO_4, filtered and concentrated under reduced pressure to afford the compound **24** (4.2g) that is used in the next step without further purification.

Step 4: Synthesis of compound 25

[0149] Hydroxylamine sulphate (2.95 g, 17.9 mmol) and solid NaOH (2.16g, 53.77mmol) are added to a stirring solution of compound **24** (3.5g, 17.9 mmol) in water (35.0 mL), and the resultant reaction mixture is stirred at reflux for 14 h. The reaction mixture is cooled to room temperature and then extracted with EtOAc (3 times). The combined EtOAc layers are washed with water, brine, dried over *anhy.* Na_2SO_4, filtered and concentrated under reduced pressure. The crude is purified by silica gel column chromatography (50% ethyla cetate in heptane) to afford 1.4 g of compound **25.** Yield: 37%, LC-MS (Method d): retention time: 1.09 min, m/z 211 [M+H].

Synthesis of compound 28

[0150]

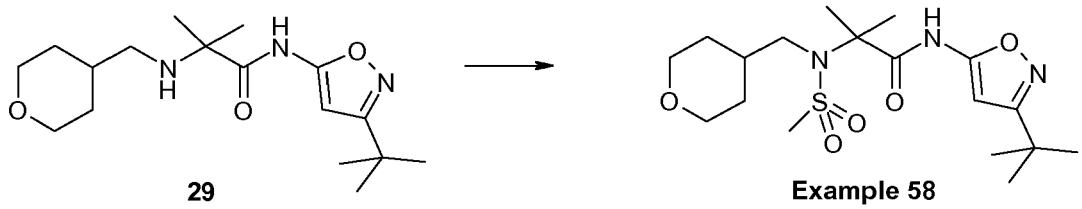


[0151] A solution of compound **26** and compound **27** in conc. HCl isheated at 100 °C for 3 h. The reaction mixture is quenched with *aq* NH_3 solution and extracted with ethyl acetate (twice). The combined EtOAc fraction is washed with brine solution, dried over *anh.* Na_2SO_4, filtered and concentrated under reduced pressure. The crude is purified by silica gel column chromatography (5% methanol in dichloromethane) to afford 0.85 g of compound **28.** Yield: 30%, LC-MS (Method d): retention time: 0.74 min, m/z 186 [M+H].

Method O:

Synthesis of Example 58:

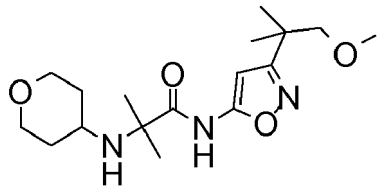
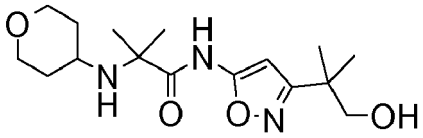
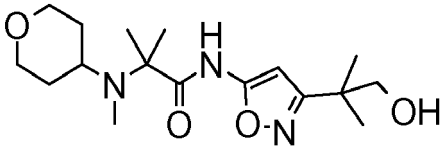
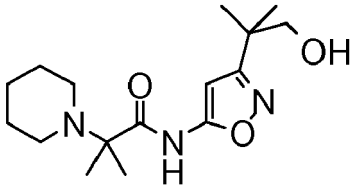
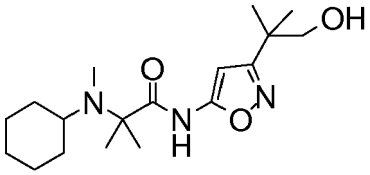
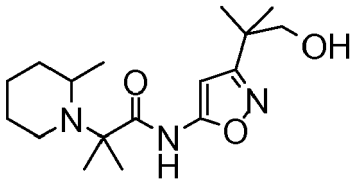
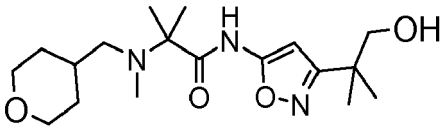
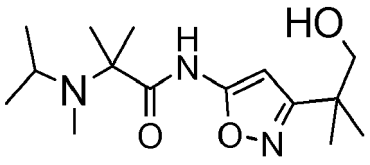
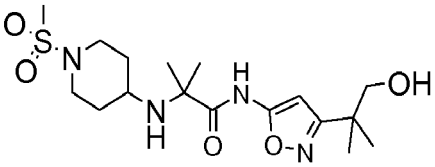
[0152]



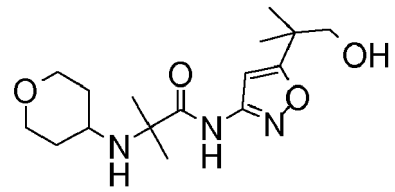
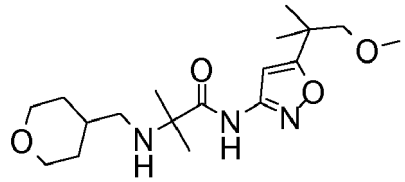
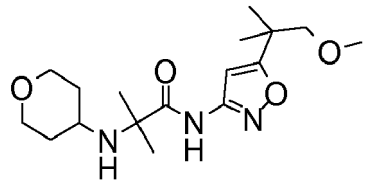
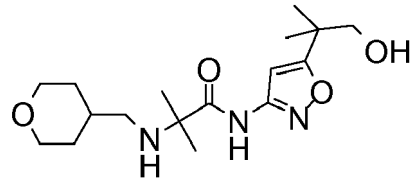
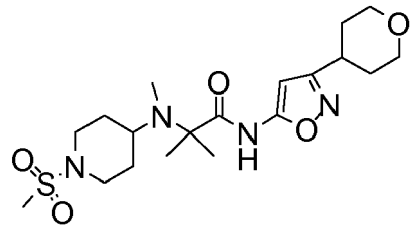
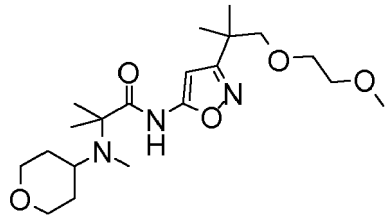
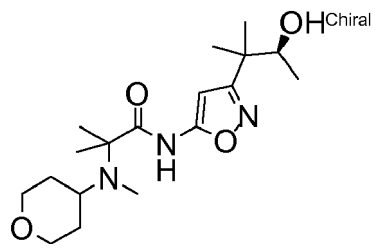
[0153] A microwave reaction vessel is charged with a solution of compound 29 (120 mg, 0.37 mmol, prepared according to WO2009105509, Boehringer Ingelheim) in THF (2 mL) and NaH (60% dispersion in mineral oil, 15mg, 0.37 mmol) is added. The mixture is stirred at room temperature for 5 min and methanesulfonylchoride (28 μL, 0.37 mmol) is added. The reaction mixture is heated in a microwave to 70 °C for 1 h. The mixture is diluted with ethyl acetate (20 mL) and washed with 1N aqueous HCl solution (2 x 3 mL) and brine (3 mL). The organic layer is dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue is dissolved in ethyl acetate and heptanes are added. The resulting white precipitate is isolated by filtration and dried under reduced pressure to afford 18 mg of example 58. Yield: 12%; LC-MS (Method a): retention time: 3.92 min, m/z 402 [M+H].

[0154] Compounds listed in Table IV under Method O are made following this procedure.

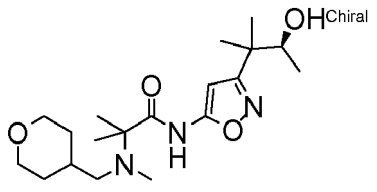
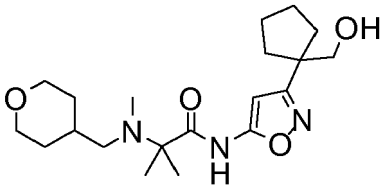
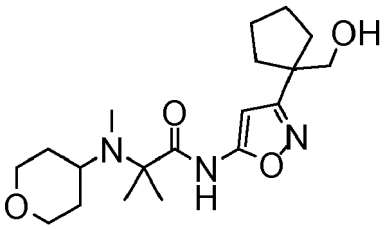
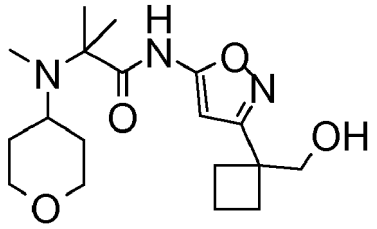
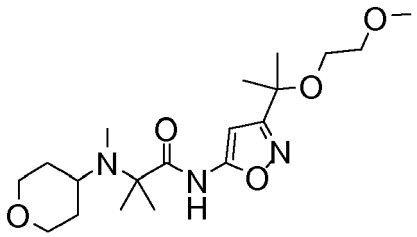
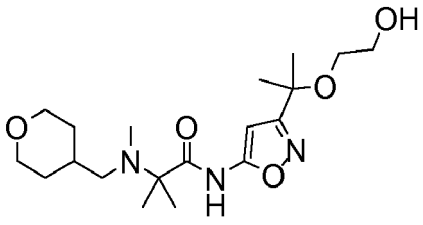
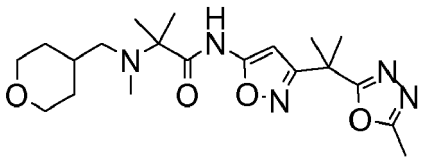
Table IV: Examples

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
1		a	2.40	340	A
2		a	2.16	326	B
3		a	2.17	340	C
4		a	2.19	310	C
5		a	2.56	338	C
6		a	2.35	324	D
7		c	0.71	354	C
8		f	0.82	298	C
9		c	0.50	403	C

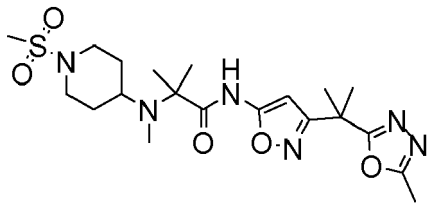
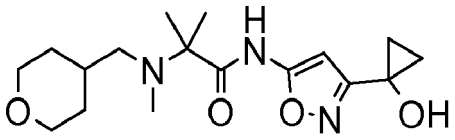
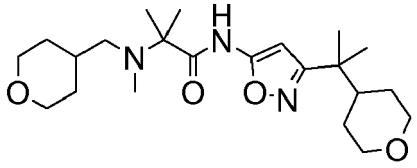
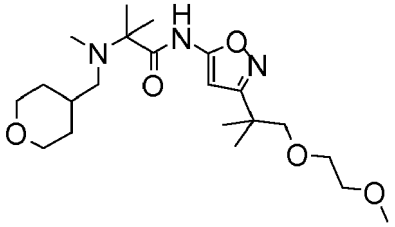
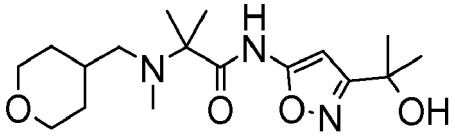
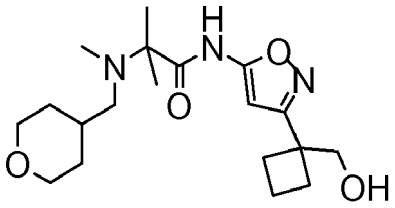
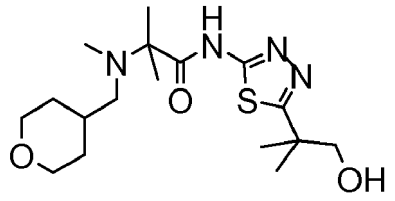
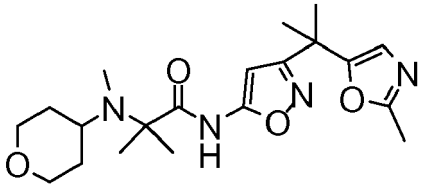
(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
10		a	2.14	326	E
11		a	2.60	354	A
12		a	2.50	340	A
13		a	2.25	340	E
14		g	4.00	429	L
15		c	0.92	398	L
16		d	0.86	354	L1

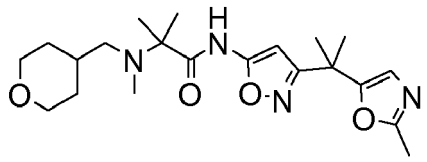
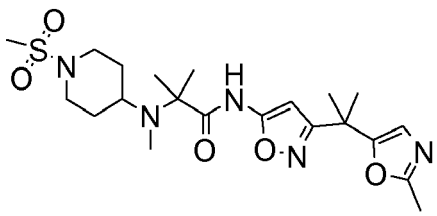
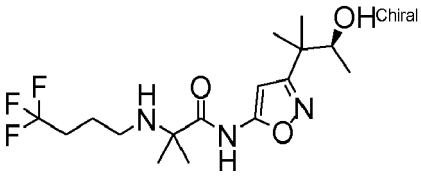
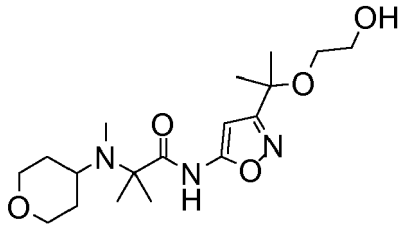
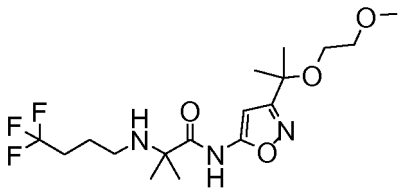
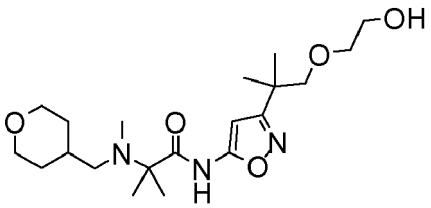
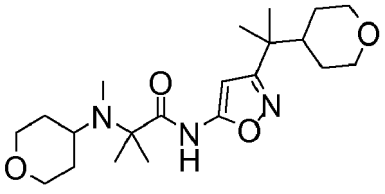
(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
17		f	0.94	368	L1
18		d	0.97	380	L1
19		d	0.93	366	L1
20		c	0.33	352	L1
21		d	1.08	384	L
22		d	0.90	384	M
23		g	3.96	406	J

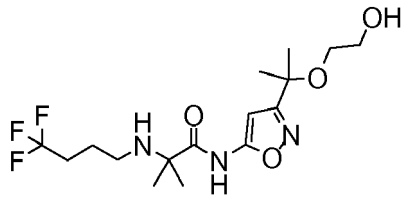
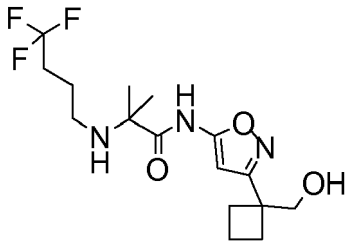
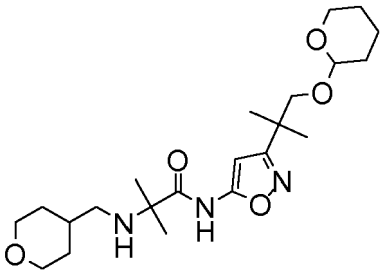
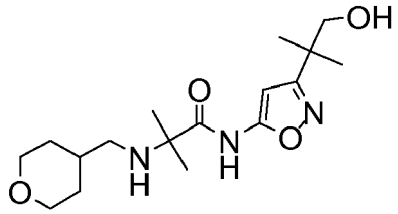
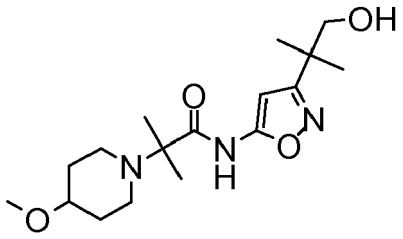
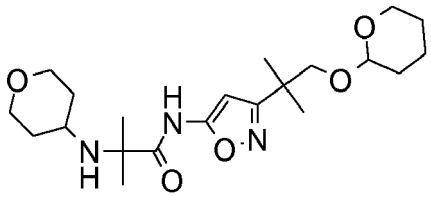
(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
24		g	3.40	469	K
25		d	0.77	338	J
26		d	1.04	408	J
27		c	0.97	412	J
28		d	0.73	340	J
29		c	0.77	366	J1
30		c	0.40	371	J2
31		g	4.03	391.7	L

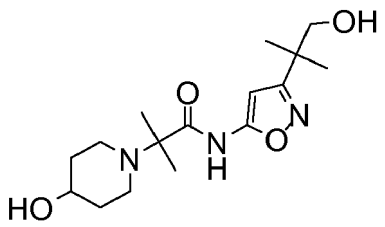
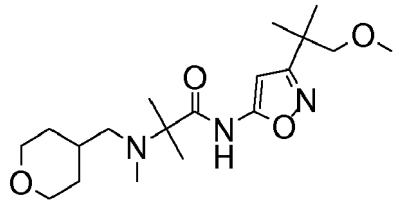
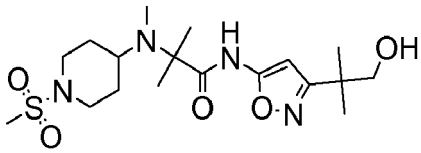
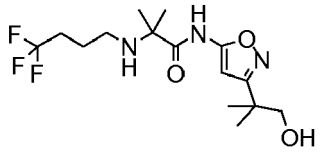
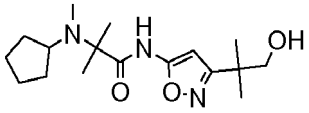
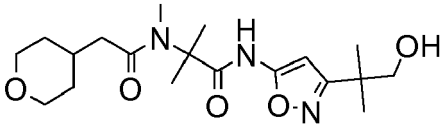
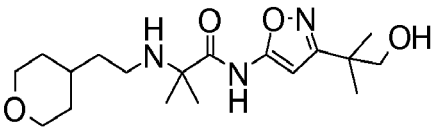
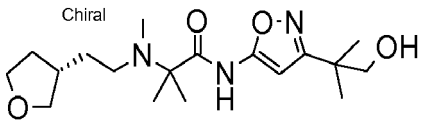
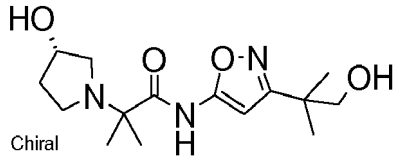
(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
32		g	4.19	405	J
33		g	4.28	468	K
34		d	0.98	366	L1
35		d	0.83	370	M
36		d	1.05	396	L
37		c	0.74	398	M
38		d	1.03	394	K

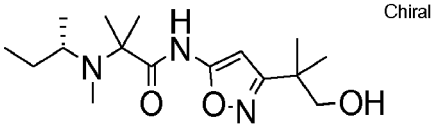
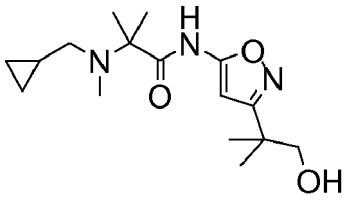
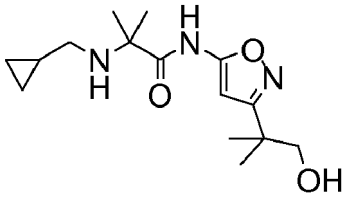
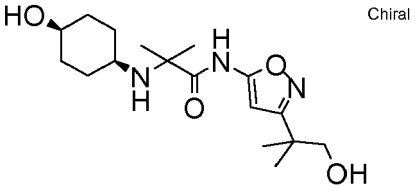
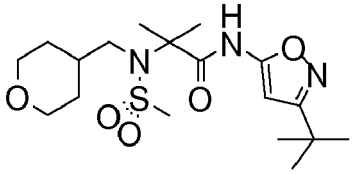
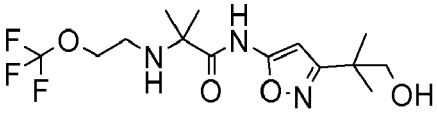
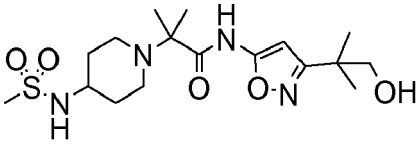
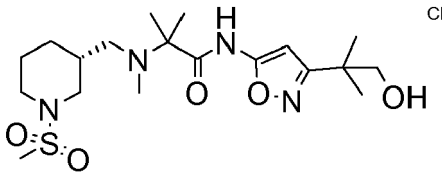
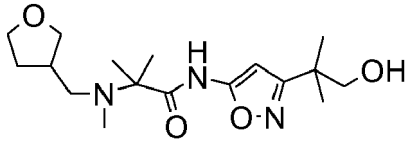
(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
39		d	0.94	382	M
40		c	0.85	364	L1
41		a	2.89	424	C
42		a	2.14	340	C
43		a	2.36	340	C
44		a	2.74	410	C

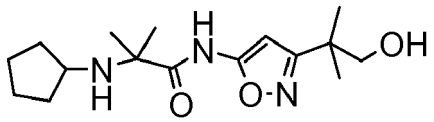
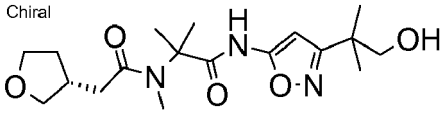
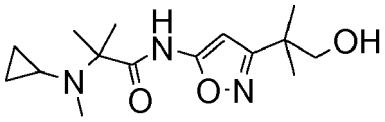
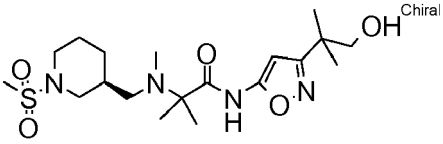
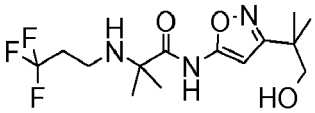
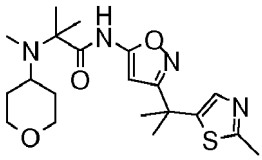
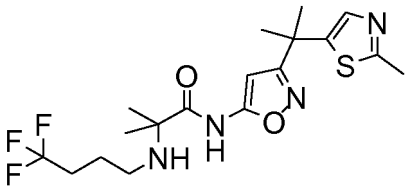
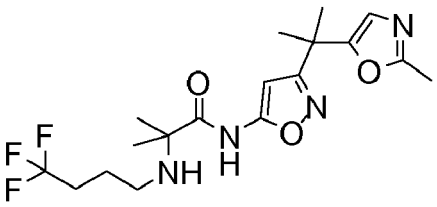
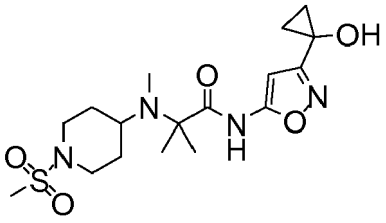
(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
45		a	1.87	326	C
46		a	2.60	368	F
47		a	2.25	417	C
48		a	2.51	352	C
49		a	2.33	324	C
50		a	3.06	382	G
51		a	2.30	354	C
52		a	2.19	354	H
53		a	1.86	312	C

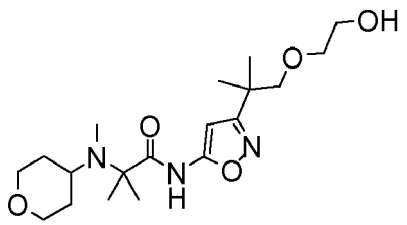
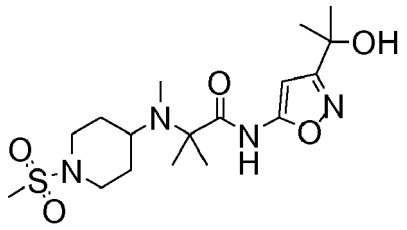
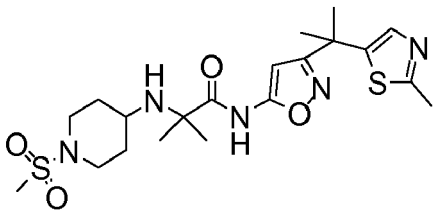
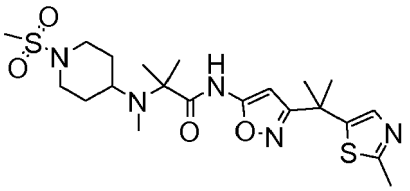
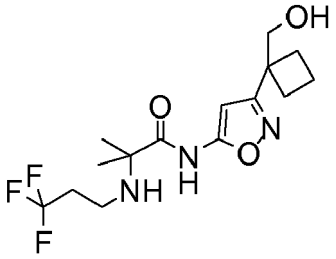
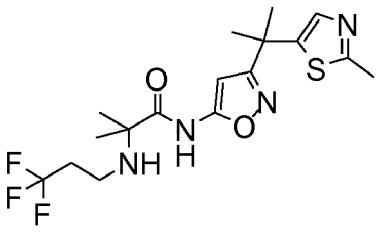
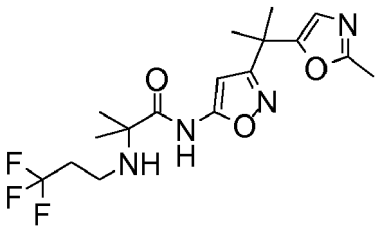
(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
54	 Chiral	a	2.35	312	I
55		a	2.24	310	I
56		a	2.18	296	C
57	 Chiral	a	2.13	340	C
58		a	3.92	402	O
60		a	2.42	354	C
61		a	2.09	403	C
62	 Ch	a	2.48	431	I
63		a	2.08	340	C

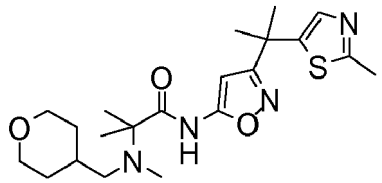
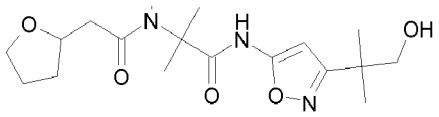
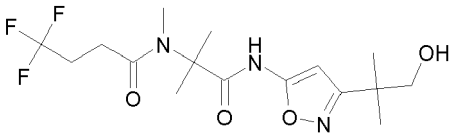
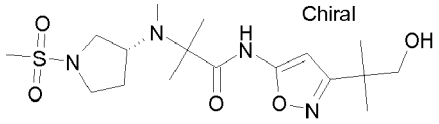
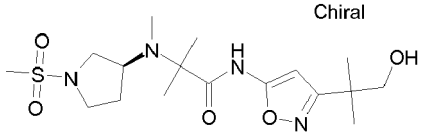
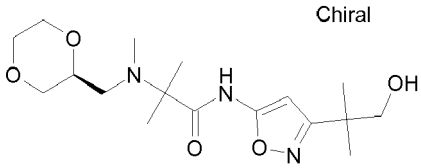
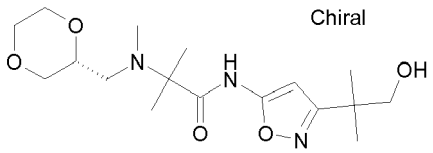
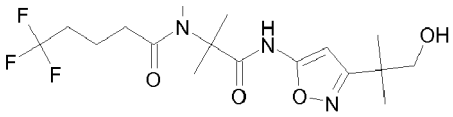
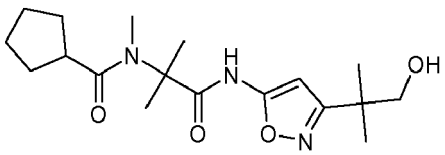
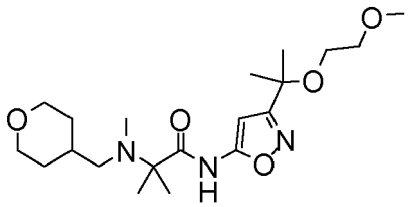
(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
64		a	2.41	310	C
65		a	2.90	368	G
66		a	2.26	296	C
67		a	2.49	431	I
68		a	2.38	338	C
69		c	0.96	407	J
71		c	0.97	419	L
72		c	0.92	403	L
73		f	0.85	401	K1

(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
74		c	0.54	384	M
75		g	4.05	403	K1
76		g	4.34	468	L
77		g	4.22	484	K
78		c	0.84	350	L
79		c	1.09	405	L
80		c	1.02	389	L

(continued)

Example #	Structure	LC Method	retention time [min]	m/z [M+H+]	Method
81		c	1.01	421	J
82		a	3.09	368	G
83		a	3.51	380	G
84		a	2.90	403	I
85		a	2.86	403	I
86		a	2.36	356	C
87		a	2.38	356	C
88		a	3.66	394	G
89		a	3.51	352	G
91		d	0.96	398	L

Analytical Methods

LC Method a:

HPLC-MS equipment

[0155] HPLC pumps: Agilent G1312A
Autoinjectors: CTC PAL HTC
Detectors:

MS: Waters ZQ
UV: Waters 2996 photodiode array

Ancillary: Waters 2420 evaporative light scattering detectors (ELS) Higher specification method designed for medicinal chemistry sample screening

Column	Waters Atlantis dC18 2.1 x100mm, 3μm column		Flow rate	0.6 ml/min
Mobile Phase	A, 0.1 % Formic acid (water)		Injection Vol	3 μl
	B, 0.1% Formic acid (CH_3CN)			
Temp.	40°C		Detection	215nm (nominal)
Gradient	Time (mins)	% organic	See Fig. ½	
	0.00	5		
	5.00	100		
	5.40	100		
	5.42	5		
	7.00	5		

LC Method b:

HPLC-MS equipment:

[0156] Shimadzu LCMS-2010EV system: (MS, pump, PDA)
Autoinjectors CTC PAL HTS autosampler
Standard method for routine high throughput analysis

Column	Atlantis dC18 2.1 x 50mm, 5μm		Flow rate	1 ml/min
Mobile Phase	A, Formic acid (aq) 0.1%		Injection Vol	3 μl
	B, Formic acid (CH_3CN) 0.1%			
Temp.	40°C		Detection	215nm (nominal)
Gradient	Time (mins)	% organic	See Fig. 2/2	
	0.00	5		
	2.50	100		
	2.70	100		
	2.71	5		
	3.00	5		

LC Method c: Column: Agilent SB-C18 1.8μm 3x50mm, 1.5mL/min flow rate

Time (min)	Water (0.1%FA)	Acetonitrile (0.1%FA)
0	88	12
0.25	70	30
0.3	60	40
1.19	5	95
1.75	0	100

LC Method d: Column: Agilent SB-AQ 1.8μm 3x50mm, 1.5mL/min flow rate

Time (min)	Water (0.1%FA)	Acetonitrile (0.1%FA)
0	95	5
0.25	50	50
0.3	30	70
1.3	10	90
1.7	0	100

LC Method e: Column: BEH C18, 1.7μm 2.1x50mm, 0.8mL/min flow rate

Time (min)	Water (0.05%FA)	Acetonitrile (0.05%FA)
0	90	10
1.19	5	95
1.7	5	95

LC Method f: Column: Agilent Zorbax C18 SB 3.5μm 4.6x30mm, 2.5mL/min flow rate

Time (min)	Water (0.1%FA)	Acetonitrile (0.1%FA)
0	95	5
1.7	5	95
2.0	5	95
2.1	95	5
2.3	95	5

LC Method g: Column: Agilent Zorbax Eclipse XDB-C8 5.0μm 4.6x150mm, 1.5mL/min flow rate

Time (min)	Water (0.1%FA)	Acetonitrile (0.1%FA)
0	95	5
2.0	95	5
7.0	10	90
9.0	5	95
9.3	95	5
10.0	95	5

LC Method h: Column: Zorbax XDB-C8 4.6x50 mm 3.5 μm, 2 mL/min flow rate

Time (min)	Water (0.05%FA)	Acetonitrile (0.05%FA)
0.0	95	5
3.5	40	60
4.5	5	95
4.7	95	5
5.0	95	5

Assessment of Biological Properties

[0157] The biological properties of the compounds of the formula I are assessed using the assays described below.

A. Human CB1 and CB2 Receptor Binding:

Experimental Method:

[0158] CB2 membranes are purchased and made from HEK293 EBNA cells stably transfected with human CB2 receptor cDNA (Perkin Elmer Life and Analytical Sciences). CB1 membranes are isolated from HEK cells stably co-transfected with human CB1 receptor and Gα16 cDNA's. The membrane preparation is bound to scintillation beads (Ysi-Poly-L-lysine SPA beads, GE Healthcare) for 4 hours at room temperature in assay buffer containing 50mM Tris, pH 7.5, 2.5mM EDTA, 5mM $MgCl_2$, 0.8% fatty acid free Bovine Serum Albumin. Unbound membrane is removed by washing in assay buffer. Membrane-bead mixture is added to 96-well assay plates in the amounts of 15ug membrane per well (CB2) or 2.5ug per well (CB1) and 1mg SPA bead per well. Compounds are added to the membrane-bead mixture in dose-response concentrations ranging from $1x\ 10^{-5}$ M to $1x10^{-10}$ M with 0.25% DMSO, final. The competition reaction is initiated with the addition of ^{3}H-CP55940 (Perkin Elmer Life and Analytical Sciences) at a final concentration of 1.5nM (CB2) or 2.5nM (CB1). The reaction is incubated at room temperature for 18hours and read on TopCount NXT plate reader. Total and non-specific binding is determined in the absence and presence of 1.25uM Win 55212 (Sigma). IC50 values for each compound are calculated as the concentration of compound that inhibits the specific binding of the radioactively labeled ligand to the receptor by 50% using the XLFit 4.1 four parameter logistic model. IC50 values are converted to inhibition constant (Ki) values using Cheng-Prusoff equation.

B. CB2R mediated modulation of cAMP synthesis:

[0159] Compounds of the invention are evaluated for their CB2 agonist or inverse agonistic activity in accordance with the following experimental method. Compounds which are shown to bind to CB2 by the binding assay described above but which are not shown to exhibit CB2R-mediated modulation of cAMP synthesis by this assay are presumed to be CB2 antagonists.

Experimental Method:

[0160] CHO cells expressing human CB2R (Euroscreen) are plated at a density of 5000 cells per well in 384 well plates and incubated overnight at 37°C. After removing the media, the cells are treated with test compounds diluted in stimulation buffer containing 1mM IBMX, 0.25% BSA and 10uM Forskolin. The assay is incubated for 30 minutes at 37°C. Cells are lysed and the cAMP concentration is measured using DiscoverX -XS cAMP kit, following the manufacturer's protocol. In this setting, agonists will decrease forskolin induced production of cAMP while inverse agonists will further increase forskolin induced production of cAMP. EC50 of agonists are calculated as follows. The maximal amount of cAMP produced by forskolin compared to the level of cAMP inhibited by 1uM CP55940 is defined as 100%. The EC50 value of each test compound is determined as the concentration at which 50% of the forskolin-stimulated cAMP synthesis is inhibited. Data is analyzed using a four-parameter logistic model. (Model 205 of XLfit 4.0).

C. CB1R mediated modulation of cAMP synthesis:

[0161] Compounds of the invention are evaluated for their CB1 agonist or inverse agonistic activity in accordance with

the following experimental method. Compounds which are shown to bind to CB1 by the binding assay described above but which are not shown to exhibit CB1R-mediated modulation of cAMP synthesis by this assay are presumed to be CB1 antagonists.

Experimental Method:

[0162] CHO cells expressing human CB1R (Euroscreen) are plated at a density of 5000 cells per well in 384 well plates and incubated overnight at 37°C. After removing the media, the cells are treated with test compounds diluted in stimulation buffer containing 1mM IBMX, 0.25% BSA and 10uM Forskolin. The assay is incubated for 30 minutes at 37°C. Cells are lysed and the cAMP concentration is measured using DiscoverX -XS cAMP kit, following the manufacturer's protocol. In this setting, agonists will decrease forskolin induced production of cAMP while inverse agonists will further increase forskolin induced production of cAMP. EC50 of agonists are calculated as follows. The maximal amount of cAMP produced by forskolin compared to the level of cAMP inhibited by 1uM CP55940 is defined as 100%. The EC50 value of each test compound is determined as the concentration at which 50% of the forskolin-stimulated cAMP synthesis is inhibited. Data is analyzed using a four-parameter logistic model. (Model 205 of XLfit 4.0).

Compounds Having Agonist Activity

[0163] Through the use of the above described assays compounds are found to exhibit agonistic activity and thus to be particularly well suited for the treatment of pain as well as for the treatment of inflammation. Preferred compounds of the invention will have an activity range of CB2 (<500nM) and CB1 (>20000).

Therapeutic Use

[0164] As can be demonstrated by the assays described above, the compounds of the invention are useful in modulating the CB2 receptor function. By virtue of this fact, these compounds have therapeutic use in treating disease-states and conditions mediated by the CB2 receptor function or that would benefit from modulation of the CB2 receptor function.

[0165] As the compounds of the invention modulate the CB2 receptor function, they have very useful anti-inflammatory and immune-suppressive activity and they can be used in patients as drugs, particularly in the form of pharmaceutical compositions as set forth below, for the treatment of disease-states and conditions.

[0166] As noted before, those compounds which are CB2 agonists can also be employed for the treatment of pain.

[0167] The agonist, antagonist and inverse agonist compounds according to the invention can be used in patients as drugs for the treatment of the following disease-states or indications that are accompanied by inflammatory processes:

(i) Lung diseases: e.g. asthma, bronchitis, allergic rhinitis, emphysema, adult respiratory distress syndrome (ARDS), pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease (COPD), asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced bronchoconstriction, occupational asthma, viral- or bacterial exacerbation of asthma, other non-allergic asthmas and "wheezy-infant syndrome", pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis;

(ii) Rheumatic diseases or autoimmune diseases or musculoskeletal diseases: all forms of rheumatic diseases, especially rheumatoid arthritis, acute rheumatic fever, and polymyalgia rheumatica; reactive arthritis; rheumatic soft tissue diseases; inflammatory soft tissue diseases of other genesis; arthritic symptoms in degenerative joint diseases (arthroses); tendinitis, bursitis, osteoarthritis, traumatic arthritis; collagenoses of any genesis, e.g., systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis, Sjögren syndrome, Still disease, Felty syndrome; and osteoporosis and other bone resorption diseases;

(iii) Allergic diseases: all forms of allergic reactions, e.g., angioneurotic edema, hay fever, insect bites, allergic reactions to drugs, blood derivatives, contrast agents, etc., anaphylactic shock (anaphylaxis), urticaria, angioneurotic edema, and contact dermatitis;

(iv) Vascular diseases: panarteritis nodosa, polyarteritis nodosa, periarteritis nodosa, arteritis temporalis, Wegner granulomatosis, giant cell arthritis, atherosclerosis, reperfusion injury and erythema nodosum;

(v) Dermatological diseases: e.g. dermatitis, psoriasis; sunburn, bums, eczema;

(vi) Renal diseases: e.g. nephrotic syndrome; and all types of nephritis, e.g., glomerulonephritis; pancreatits;

(vii) Hepatic diseases: e.g. acute liver cell disintegration; acute hepatitis of various genesis, e.g., viral, toxic, drug-induced; and chronically aggressive and/or chronically intermittent hepatitis;

(viii) Gastrointestinal diseases: e.g. inflammatory bowel diseases, irritable bowel syndrome, regional enteritis (Crohns disease), colitis ulcerosa; gastritis; aphthous ulcer, celiac disease, regional ileitis, gastroesophageal reflux disease;

(ix) Neuroprotection: e.g. in the treatment of neurodegeneration following stroke; cardiac arrest; pulmonary bypass; traumatic brain injury; spinal cord injury or the like;

(x) Eye diseases: allergic keratitis, uveitis, or iritis; conjunctivitis; blepharitis; neuritis nervi optici; choroiditis; glaucoma and sympathetic ophthalmia;
(xi) Diseases of the ear, nose, and throat (ENT) area: e.g. tinnitus; allergic rhinitis or hay fever; otitis externa; caused by contact eczema, infection, etc.; and otitis media;
(xii) Neurological diseases: e.g. brain edema, particularly tumor-related brain edema; multiple sclerosis; acute encephalomyelitis; meningitis; acute spinal cord injury; trauma; dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease; Parkinson's disease and Creutzfeldt-Jacob disease; Huntington's chorea, Pick's disease; motor neuron disease), vascular dementia (including multi-infarct dementia) as well as dementia associated with intracranial space occupying lesions; infections and related conditions (including HIV infection); Guillain-Barre syndrome; myasthenia gravis, stroke; and various forms of seizures, e.g., nodding spasms;
(xiii) Blood diseases: acquired hemolytic anemia; aplastic anemia, and idiopathic thrombocytopenia;
(xiv) Tumor diseases: acute lymphatic leukemia; Hodgkin's disease, malignant lymphoma; lymphogranulomatoses; lymphosarcoma; solid malignant tumors; extensive metastases,;
(xv) Endocrine diseases: endocrine ophthalmopathy; endocrine orbitopathia; thyrotoxic crisis; Thyroiditis de Quervain; Hashimoto thyroiditis; Morbus Basedow; granulomatous thyroiditis; struma lymphomatosa; and Graves disease; type I diabetes (insulin-dependent diabetes);
(xvi) Organ and tissue transplantations and graft-versus-host diseases;
(xvii) Severe states of shock, e.g., septic shock, anaphylactic shock, and systemic inflammatory response syndrome (SIRS);
(xviii) Acute pain such as dental pain, perioperative, post-operative pain, traumatic pain, muscle pain, pain in burned skin, sun burn, trigeminal neuralgia, sun burn; spasm of the gastrointestinal tract or uterus, colics;
(xix) Visceral pain such as pain associated with chronic pelvic pain, pancreatitis, peptic ulcer, interstitial cystitis, renal colic, angina, dysmenorrhoea, menstruation, gynaecological pain, irritable bowel syndrome (IBS), non-ulcer dyspepsia, non-cardiac chest pain, myocardial ischemia;
(xx) Neuropathic pain such as low back pain, non-herpetic neuralgia, post herpetic neuralgia, diabetic neuropathy, nerve injury, acquired immune deficiency syndrome (AIDS) related neuropathic pain, head trauma, painful traumatic mononeuropathy, toxin and chemotherapy induced pain, phantom limb pain, painful polyneuropathy, thalamic pain syndrome, post-stroke pain, central nervous system injury, post surgical pain, stump pain, repetitive motion pain, pain induced by post mastectomy syndrome, multiple sclerosis, root avulsions, postthoracotomy syndrome, neuropathic pain associated hyperalgesia and allodynia.
(xxi) Inflammatory/nociceptive pain induced by or associated with disorders such as osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis, gout, vulvodynia, myofascial pain (muscular injury, fibromyalgia), tendonitis, osteoarthritis, juvenile arthritis, spondylitis, gouty arthritis, psoriatic arthritis, muscoskeletal pain, fibromyalgia, sprains and strains, sympathetically maintained pain, myositis, pain associated with migraine, toothache, influenza and other viral infections such as the common cold, rheumatic fever, systemic lupus erythematosus;
(xxii) Cancer pain induced by or associated with tumors such as lymphatic leukemia; Hodgkin's disease, malignant lymphoma; lymphogranulomatoses; lymphosarcoma; solid malignant tumors; extensive metastases;
(xxiii) Headache such as cluster headache, migraine with and without aura, tension type headache, headache with different origins, headache disorders including prophylactic and acute use;
(xxiv) various other disease-states or conditions including, restenosis following percutaneous transluminal coronary angioplasty, acute and chronic pain, atherosclerosis, reperfusion injury, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion, sarcoidosis, gingivitis, pyrexia. edema resulting from trauma associated with bums, sprains or fracture, cerebral oedema and angioedema, Diabetes such as diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hypergiycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion).

[0168] Other indications include: epilepsy, septic shock e.g. as antihypovolemic and/or antihypotensive agents, cancer, sepsis, osteoporosis, benign prostatic hyperplasia and hyperactive bladder, pruritis, vitiligo, general gastrointestinal disorders, disturbances of visceral motility at respiratory, genitourinary, gastrointestinal or vascular regions, wounds, bums, tissue damage and postoperative fever, syndromes associated with Itching.

[0169] Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like.

[0170] For treatment of the above-described diseases and conditions, a therapeutically effective dose will generally be in the range from about 0.01 mg to about 100 mg/kg of body weight per dosage of a compound of the invention; preferably, from about 0.1 mg to about 20 mg/kg of body weight per dosage. For example, for administration to a 70 kg person, the dosage range would be from about 0.7 mg to about 7000 mg per dosage of a compound of the invention, preferably from about 7.0 mg to about 1400 mg per dosage. Some degree of routine dose optimization may be required

to determine an optimal dosing level and pattern. The active ingredient may be administered from 1 to 6 times a day.

General Administration and Pharmaceutical Compositions

[0171] When used as pharmaceuticals, the compounds of the invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the invention. The compounds of the invention may also be administered alone or in combination with adjuvants that enhance stability of the compounds of the invention, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increased inhibitory activity, provide adjunct therapy, and the like. The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. In general, the compounds of this invention are administered in a therapeutically or pharmaceutically effective amount, but may be administered in lower amounts for diagnostic or other purposes.

[0172] Administration of the compounds of the invention, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted modes of administration of pharmaceutical compositions. Thus, administration can be, for example, orally, buccally (e.g., sublingually), nasally, parenterally, topically, transdermally, vaginally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The pharmaceutical compositions will generally include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, vehicles, or combinations thereof. Such pharmaceutically acceptable excipients, carriers, or additives as well as methods of making pharmaceutical compositions for various modes or administration are well-known to those of skill in the art. The state of the art is evidenced, e.g., by Remington: The Science and Practice of Pharmacy, 20th Edition, A. Gennaro (ed.), Lippincott Williams & Wilkins, 2000; Handbook of Pharmaceutical Additives, Michael & Irene Ash (eds.), Gower, 1995; Handbook of Pharmaceutical Excipients, A.H. Kibbe (ed.), American Pharmaceutical Ass'n, 2000; H.C. Ansel and N.G. Popovish, Pharmaceutical Dosage Forms and Drug Delivery Systems, 5th ed., Lea and Febiger, 1990; each of which is incorporated herein by reference in their entireties to better describe the state of the art.

[0173] As one of skill in the art would expect, the forms of the compounds of the invention utilized in a particular pharmaceutical formulation will be selected (e.g., salts) that possess suitable physical characteristics (e.g., water solubility) that is required for the formulation to be efficacious.

[0174] Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[0175] Pharmaceutical compositions suitable for parenteral administration comprise sterile aqueous preparations of a compound of the present invention. These preparations are preferably administered intravenously, although administration can also be effected by means of subcutaneous, intramuscular, or intradermal injection. Injectable pharmaceutical formulations are commonly based upon injectable sterile saline, phosphate-buffered saline, oleaginous suspensions, or other injectable carriers known in the art and are generally rendered sterile and isotonic with the blood. The injectable pharmaceutical formulations may therefore be provided as a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, including 1,3-butanediol, water, Ringer's solution, isotonic sodium chloride solution, fixed oils such as synthetic mono- or diglycerides, fatty acids such as oleic acid, and the like. Such injectable pharmaceutical formulations are formulated according to the known art using suitable dispersing or setting agents and suspending agents. Injectable compositions will generally contain from 0.1 to 5% w/w of a compound of the invention.

[0176] Solid dosage forms for oral administration of the compounds include capsules, tablets, pills, powders, and granules. For such oral administration, a pharmaceutically acceptable composition containing a compound(s) of the invention is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, pregelatinized starch, magnesium stearate, sodium saccharine, talcum, cellulose ether derivatives, glucose, gelatin, sucrose, citrate, propyl gallate, and the like. Such solid pharmaceutical formulations may include formulations, as are well-known in the art, to provide prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms, which include, but are not limited to, pH sensitive release from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form.

[0177] Liquid dosage forms for oral administration of the compounds include emulsions, microemulsions, solutions, suspensions, syrups, and elixirs, optionally containing pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like. These compositions can also contain additional adjuvants such

as wetting, emulsifying, suspending, sweetening, flavoring, and perfuming agents.

[0178] Topical dosage forms of the compounds include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, eye ointments, eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. Topical application may be once or more than once per day depending upon the usual medical considerations. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation, more usually they will form up to about 80% of the formulation.

[0179] Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal administration can be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Such patches suitably contain a compound of the invention in an optionally buffered, aqueous solution, dissolved and/or dispersed in an adhesive, or dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%.

[0180] For administration by inhalation, the compounds of the invention are conveniently delivered in the form of an aerosol spray from a pump spray device not requiring a propellant gas or from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide, or other suitable gas. In any case, the aerosol spray dosage unit may be determined by providing a valve to deliver a metered amount so that the resulting metered dose inhaler (MDI) is used to administer the compounds of the invention in a reproducible and controlled way. Such inhaler, nebulizer, or atomizer devices are known in the prior art, for example, in PCT International Publication Nos. WO 97/12687 (particularly Figure 6 thereof, which is the basis for the commercial RESPIMAT® nebulizer); WO 94/07607; WO 97/12683; and WO 97/20590, to which reference is hereby made and each of which is incorporated herein by reference in their entireties.

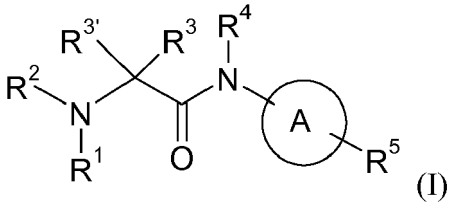
[0181] Rectal administration can be effected utilizing unit dose suppositories in which the compound is admixed with low-melting water-soluble or insoluble solids such as fats, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, or fatty acid esters of polyethylene glycols, or the like. The active compound is usually a minor component, often from about 0.05 to 10% by weight, with the remainder being the base component.

[0182] In all of the above pharmaceutical compositions, the compounds of the invention are formulated with an acceptable carrier or excipient. The carriers or excipients used must, of course, be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the patient. The carrier or excipient can be a solid or a liquid, or both, and is preferably formulated with the compound of the invention as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compound. Such carriers or excipients include inert fillers or diluents, binders, lubricants, disintegrating agents, solution retardants, resorption accelerators, absorption agents, and coloring agents. Suitable binders include starch, gelatin, natural sugars such as glucose or β-lactone, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

[0183] Pharmaceutically acceptable carriers and excipients encompass all the foregoing additives and the like.

Claims

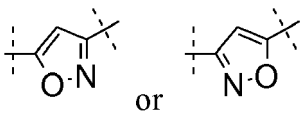
1. A compound of the formula (I)



(I)

wherein:

ring A is



R^1 is hydrogen, C_{1-10} alkyl or C_{3-10} cycloalkyl which is optionally substituted with 1-3 C_{1-10} alkyl, each **R^1** or it's substituent is optionally halogenated;

R^2 is C_{1-6} alkyl, C_{3-7} cycloalkyl, 1,1-dioxo-1λ^6-thiomorpholinylcarbonyl, phenylsulfonyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl or piperidinyl, each optionally independently substituted with 1 to 3 substituents chosen from C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{1-5} alkoxy, C_{1-5} alkylthio, C_{1-5} alkylsulfonyl, C_{1-5} alkoxycarbonyl, C_{1-5} alkylamino, C_{3-6} cycloalkylamino, C_{1-5} dialkylamino, C_{1-5} alkylaminocarbonyl, C_{1-5} acylamino, C_{1-5} dialkylaminocarbonyl, hydroxyl, halogen, cyano, nitro, oxo, phenyl and heterocyclyl chosen from tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl and piperazinyl, each R^2 substituent where possible is optionally halogenated or substituted with 1 to 3 C_{1-5} alkyl, C_{1-5} acyl, methyl sulfonyl, cyano, phenyl, oxo or hydroxyl;

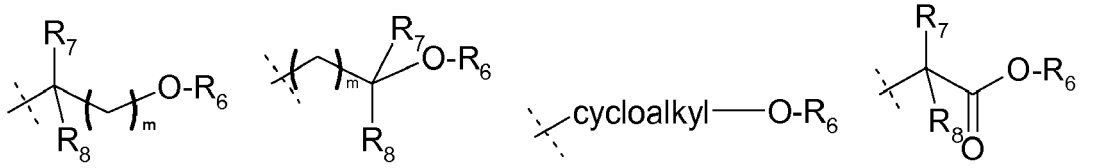
or **R^1** and **R^2** together with the nitrogen atom to which they are attached form a ring chosen from thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, azetidinyl, benzimidazolyl, pyrazolyl, imidazolyl, triazinyl, indazolyl, indolyl, indolinyl, isoindolyl, isoindolinyl, and 2-aza-spiro[4.5]dec-2-yl, 1-aza-spiro[4.5]dec-1-yl, 1-aza-spiro[4.4]non-1-yl, 2-aza-spiro[4.4]non-2-yl, 2-aza-spiro[5.5]undec-2-yl, 1-aza-spiro[5.5]undec-1-yl,

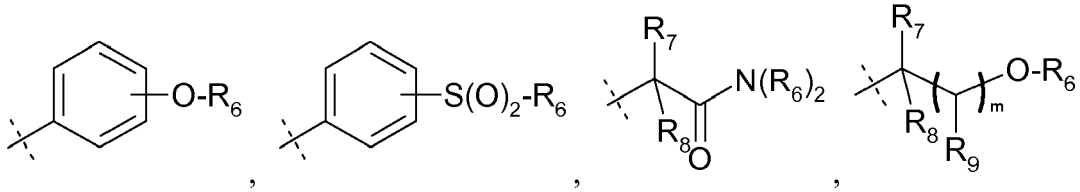
each optionally substituted with 1 to 3 C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, C_{1-6} alkyl sulfonyl, cyano, phenyl, oxo, hydroxyl and halogen each ring substituent being further optionally halogenated where possible;

R^3 and **$R^{3'}$** are each methyl or ethyl, each optionally halogenated, or R^3 and R^4 together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring each optionally halogenated.

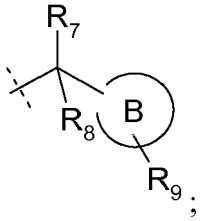
R^4 is hydrogen or methyl;

R^5 is chosen from





and



m is 0, 1, 2 or 3;

R^6 is hydrogen, C_{1-4} alkyl or C_{1-4} alkoxy;

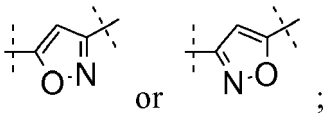
R^7 and **R^8** are each independently hydrogen, or C_{1-4} alkyl with the proviso that both R^7 and R^8 cannot be

hydrogen; and wherein **R7** and **R8** optionally can cyclize to form a C_{3-7} cycloalkyl ring;
R9 is C_{1-6} alkyl or aryl;
ring B is a 5-6 membered heterocyclic ring;
n is 0, 1 or 2;

wherein any carbon atom on the formula (I) or any R substituent listed above is optionally partially or fully halogenated where possible;
or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 and wherein

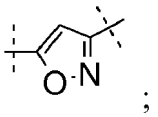
ring A is



R1 is hydrogen or C_{1-3} alkyl optionally halogenated;
R2 is C_{1-6} alkyl or C_{3-7} cycloalkyl optionally independently substituted with 1 to 3 halogen, one C_{3-7} cycloalkyl, C_{1-6} alkoxy or one heterocyclyl chosen from tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl and piperazinyl each optionally halogenated or substituted with C_{1-4} alkyl or methyl sulfonyl;
or **R1** and **R2** together with the nitrogen atom to which they are attached form a ring chosen form thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, azetidinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, and 2-aza-spiro[4.5]dec-2-yl each optionally substituted with 1 to 3 C_{1-4} alkyl, C_{1-4} alkoxy and halogen each ring substituent being further optionally halogenated where possible;
R3 and **R3'** are each methyl or ethyl or R^3 and R^4 together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring;
R6 is hydrogen or C_{1-2} alkyl;
R7 and **R8** are each C_{1-2} alkyl.

3. The compound according to claim 2 and wherein

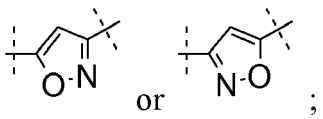
ring A is



R2 is methyl optionally substituted with one heterocyclyl chosen from tetrahydropyranyl, dioxanyl, tetrahydrofuranyl, thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl and piperazinyl each optionally halogenated or substituted with C_{1-4} alkyl or methyl sulfonyl;
or **R1** and **R2** together with the nitrogen atom to which they are attached form a ring chosen form thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, azetidinyl, indolyl and 2-aza-spiro[4.5]dec-2-yl each optionally substituted with 1 to 3 C_{1-3} alkyl, C_{1-3} alkoxy and halogen each ring substituent being further optionally halogenated where possible.

4. The compound according to claim 2, and wherein

ring A is

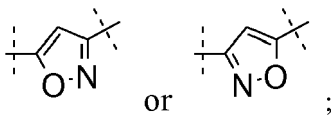


;

R^3 and **$R^{3'}$** are methyl;
R^6 is hydrogen or C_{1-2} alkyl;
wherein **R^7** and **R^8** are each C_{1-2} alkyl.

5. The compound according to claim 4, and wherein

ring A is

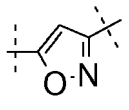


;

R^1 and **R^2** together with the nitrogen atom to which they are attached form a ring chosen from thiomorpholinyl, 1,1-dioxo-1λ^6-thiomorpholinyl, morpholinyl, pyrrolidinyl, piperidinyl, azetidinyl, indolyl and 2-aza-spiro[4.5]dec-2-yl each optionally substituted with 1 to 3 C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy and halogen each ring substituent being further optionally halogenated where possible.

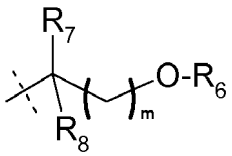
6. The compound according to claim 1, and wherein

R^2 is CF_3-CH_2-CH_2-CH_2-, CH_3-CH_2-CH_2(CH_3)-, cyclopropyl-CH_2-, hydroxylcyclohexyl, tetrahydrofuranyl-CH_2-;
ring A is



;

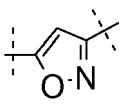
R^5 is



wherein wherein **R^7** and **R^8** optionally can cyclize to form a C_{3-7} cycloalkyl ring.

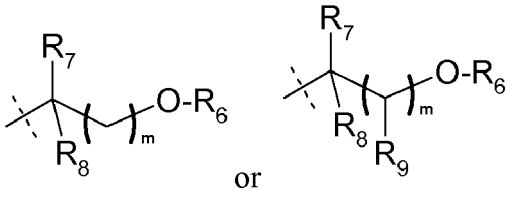
7. The compound according to claim 1, and wherein

R^2 hydroxylcyclohexyl, tetrahydropyranyl, hydroxylpyrrolidinyl or methylsulfonylpyrrolidinyl;
ring A is



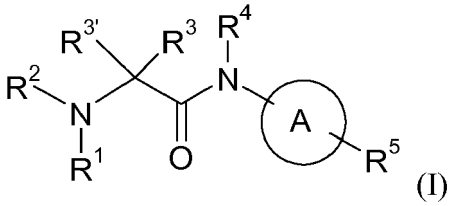
;

R^5 is

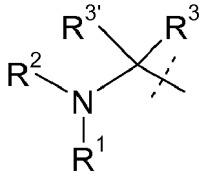


wherein wherein **R^7** and **R^8** optionally can cyclize to form a C_{3-7} cycloalkyl ring;
R^1 and **R^2** optionally can cyclize to form piperidinyl, methylsulfonylpiperidinyl.

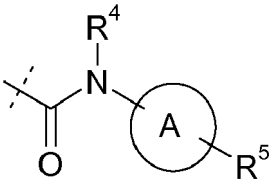
8. The compound according to any one of the preceding claims, namely a compound the formula (I)



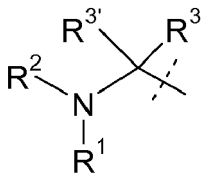
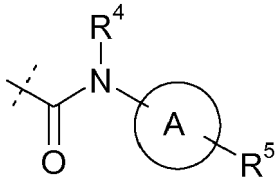
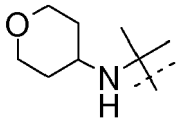
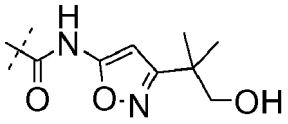
wherein



of the formula (II) is chosen from column A1 - A42 in the table, and



of the formula (II) is chosen from column B1 - B22 in the table, with the proviso that when column B is B3, B13 or B22, then A must be A20, A23, A38, or A42

			
A1		B1	

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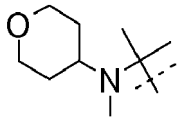
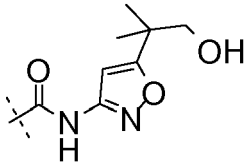
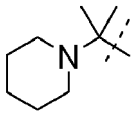
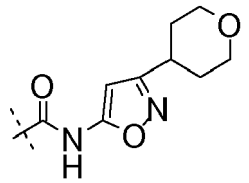
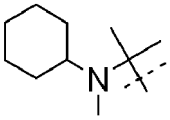
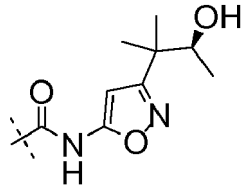
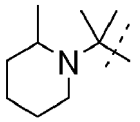
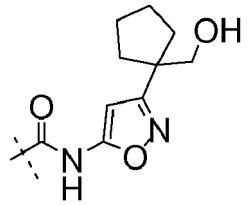
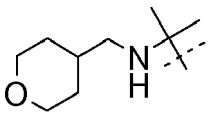
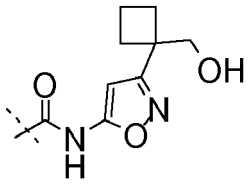
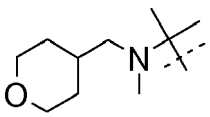
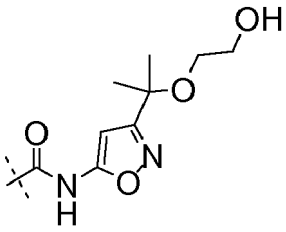
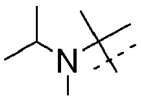
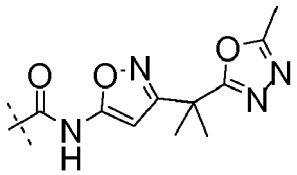
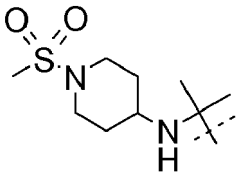
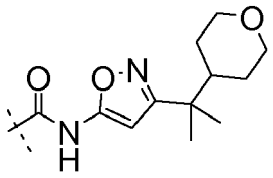
A2		B2	
A3		B3	
A4		B4	
A5		B5	
A6		B6	
A7		B7	
A8		B8	
A9		B9	

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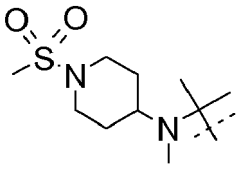
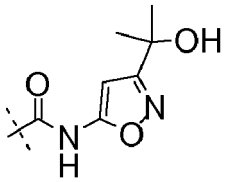
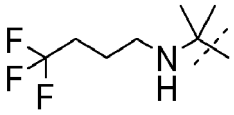
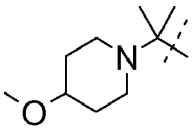
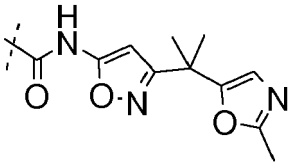
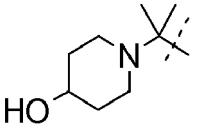
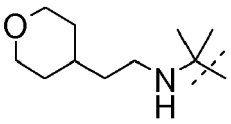
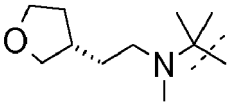
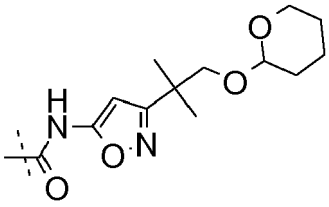
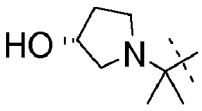
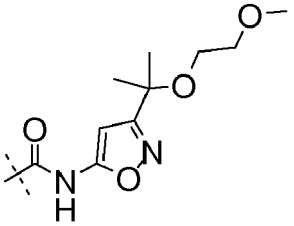
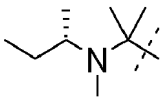
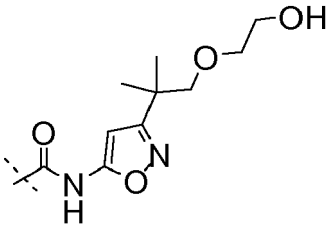
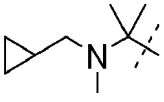
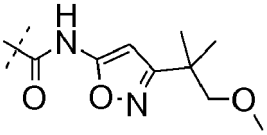
A10		B10	
A11			
A12		B12	
A13			
A14		B14	
A15		B15	
A16		B16	
A17		B17	
A18		B18	

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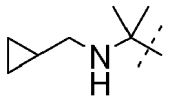
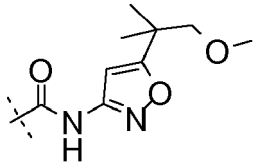
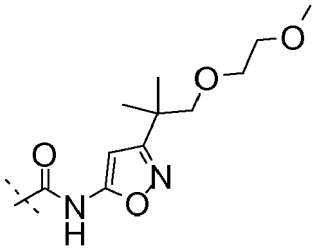
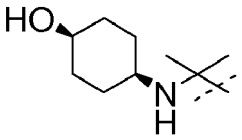
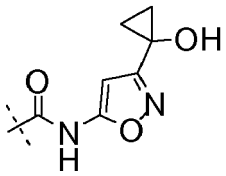
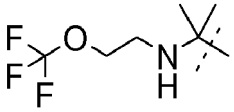
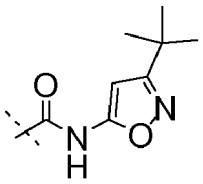
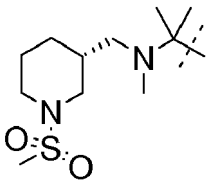
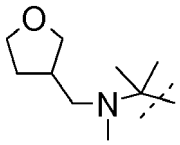
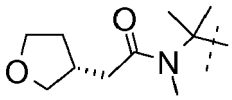
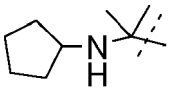
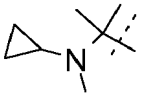
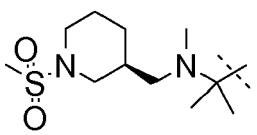
A19		B19	
		B20	
A21		B21	
A22		B22	
A24			
A25			
A26			
A27			
A28			
A29			

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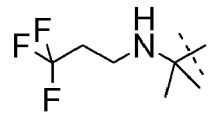
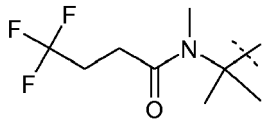
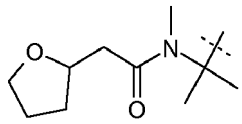
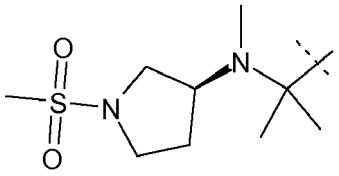
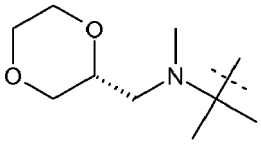
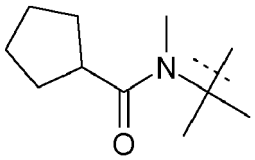
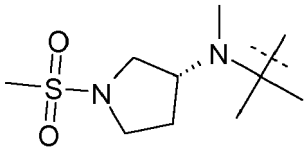
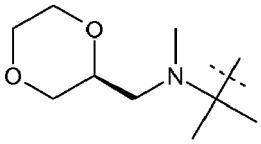
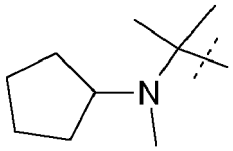
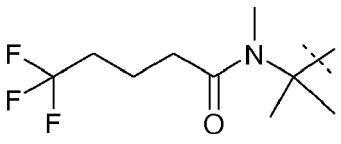
A30			
A31			
A32			
A33			
A34			
A35			
A36			
A37			
A39			
A40			

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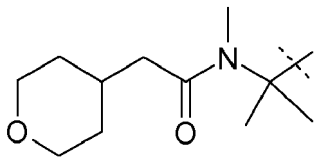
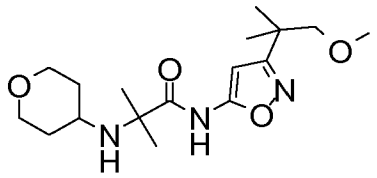
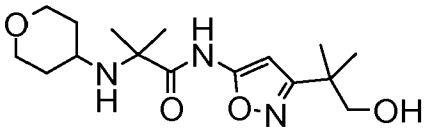
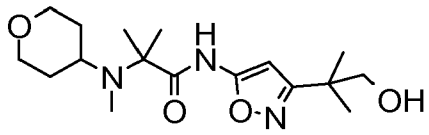
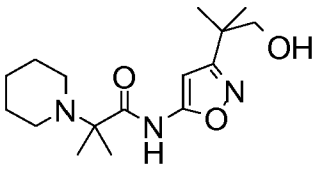
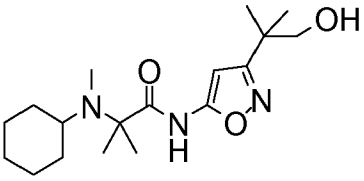
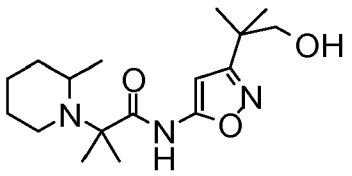
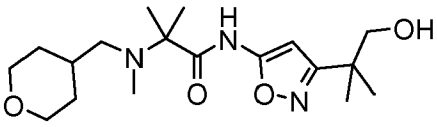
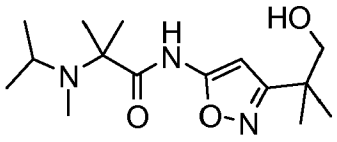
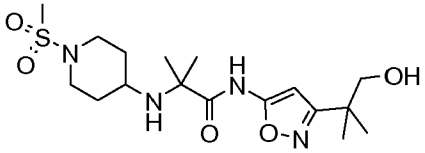
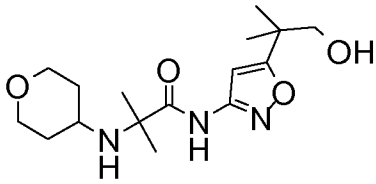
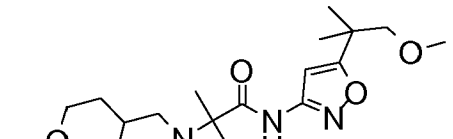
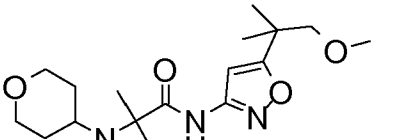
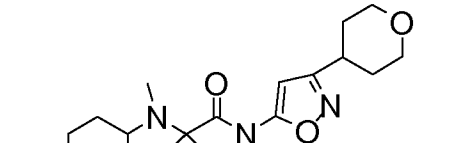
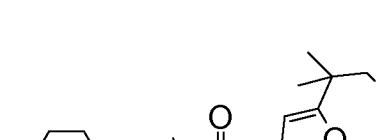
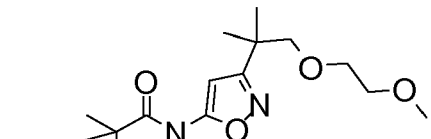
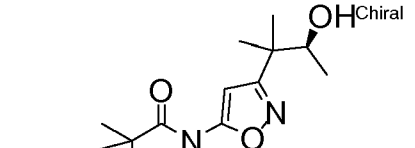
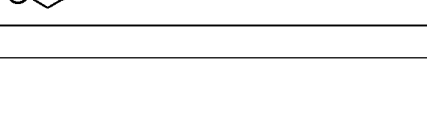
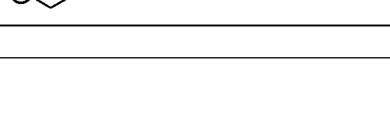
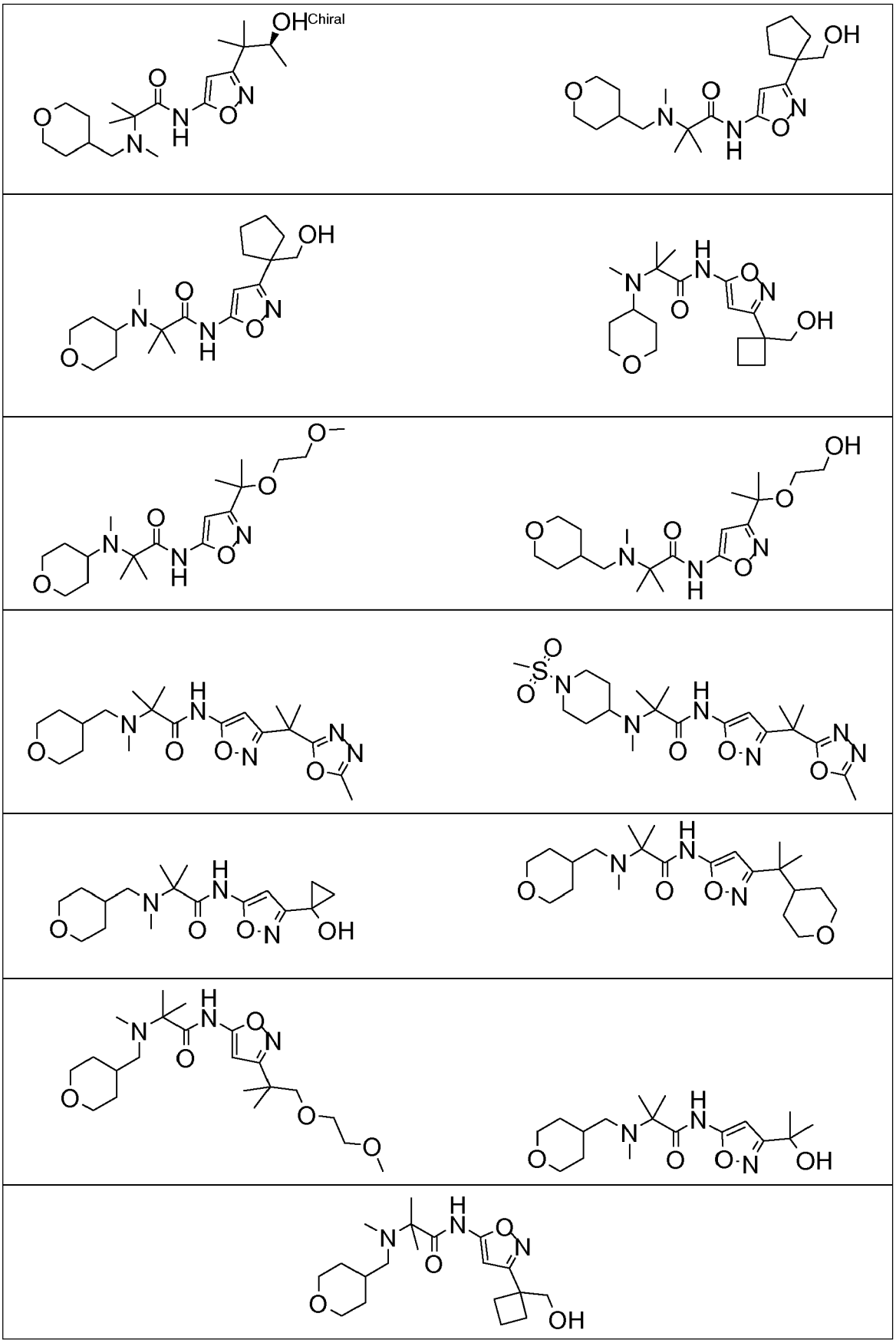
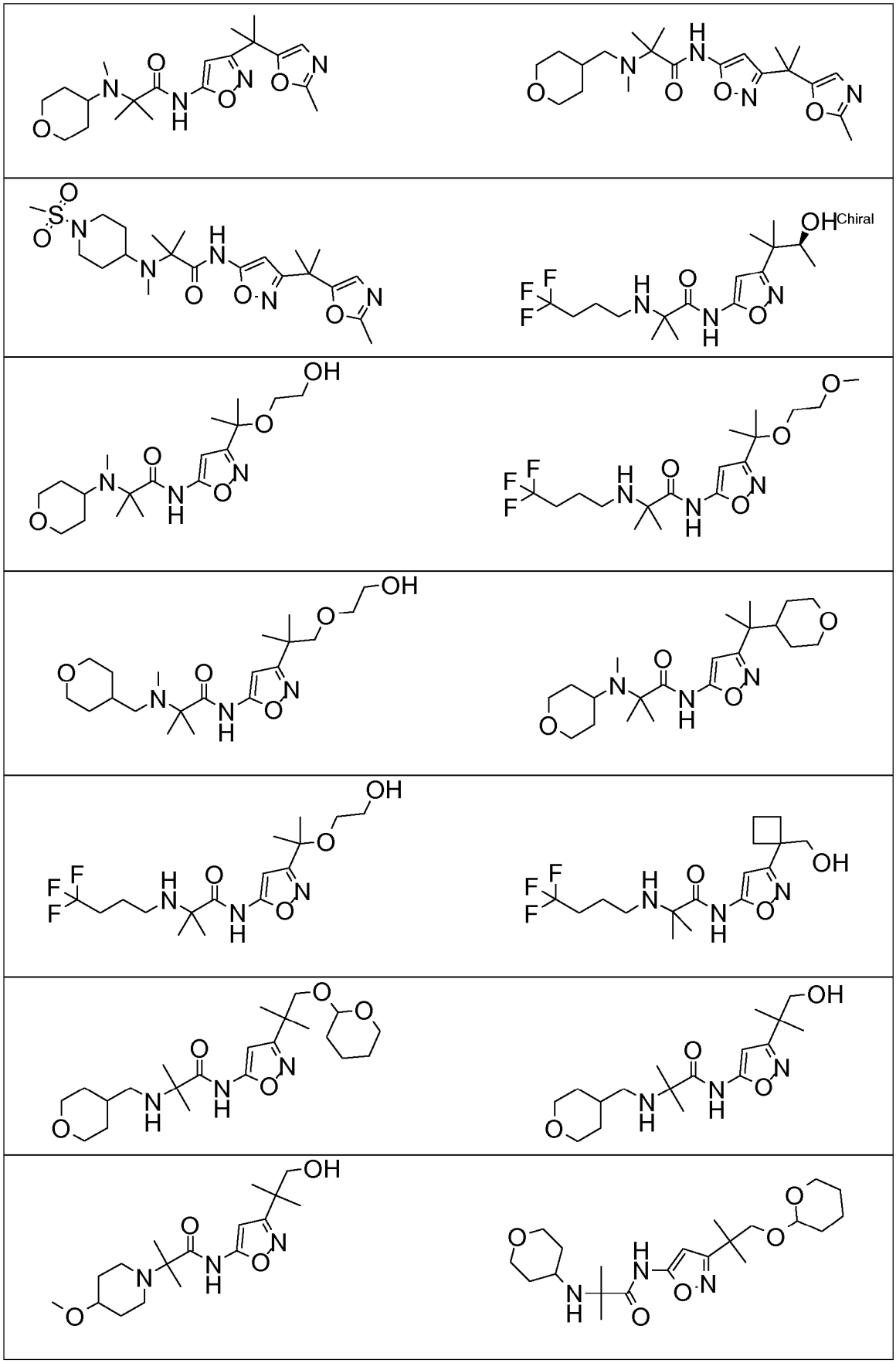
A41			

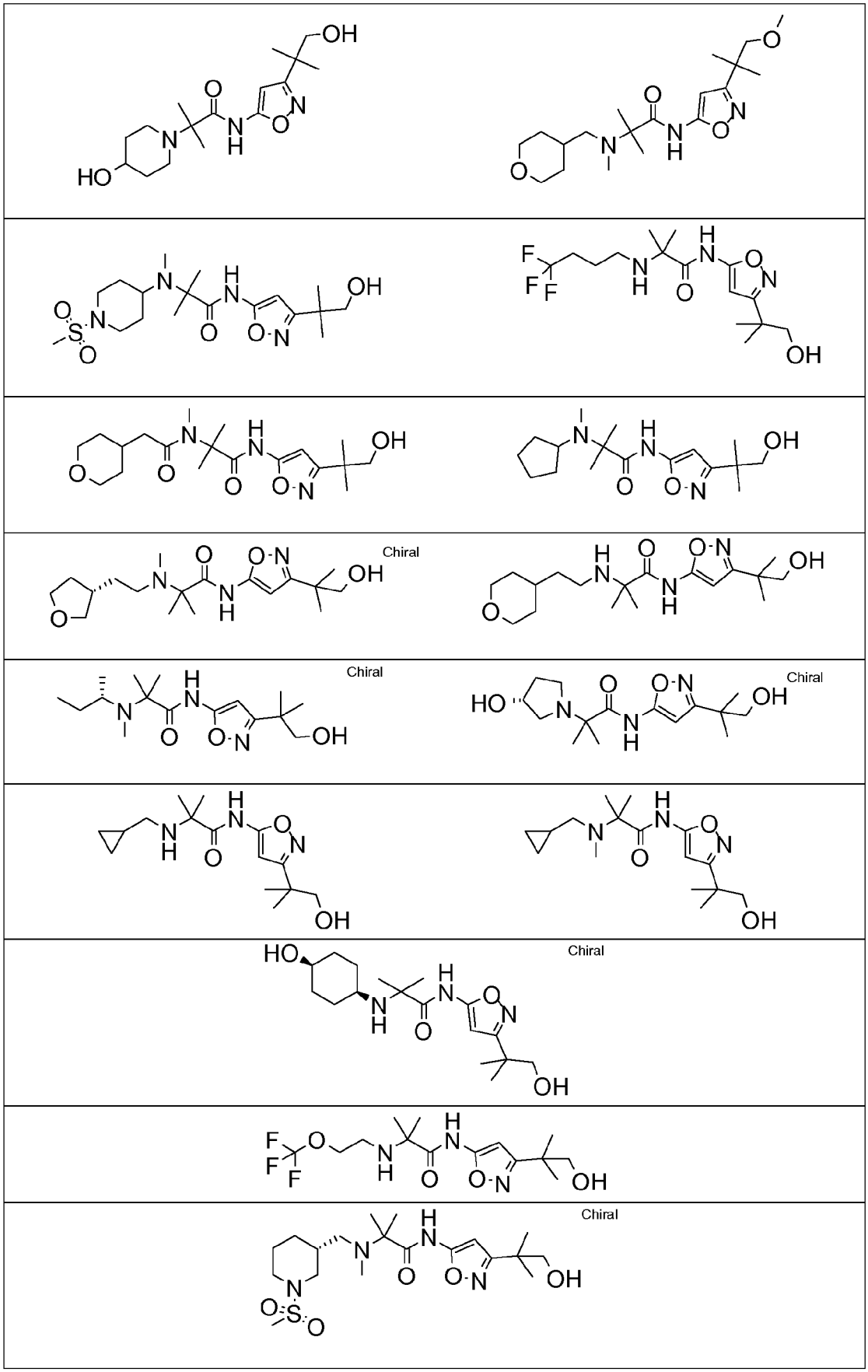
or a pharmaceutically acceptable salt thereof.

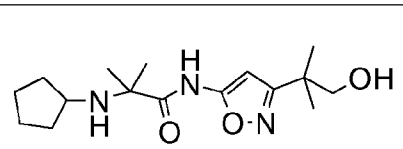
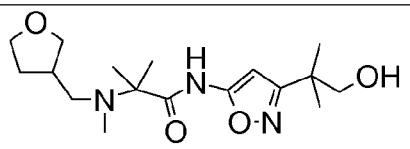
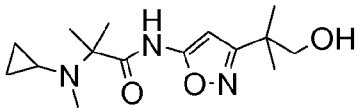
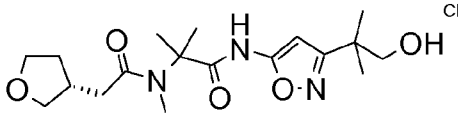
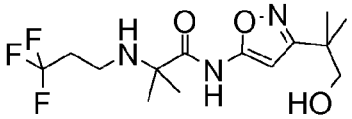
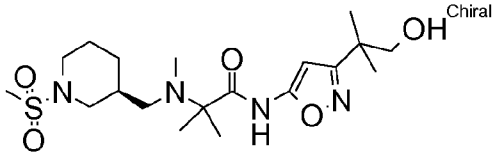
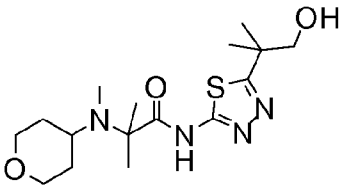
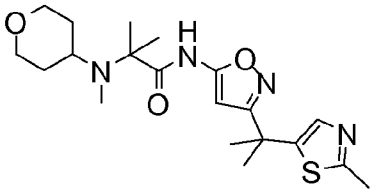
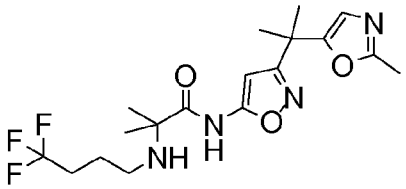
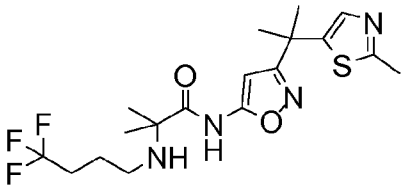
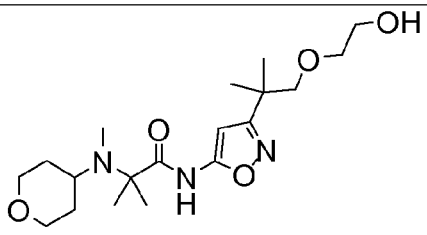
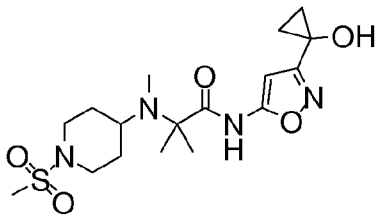
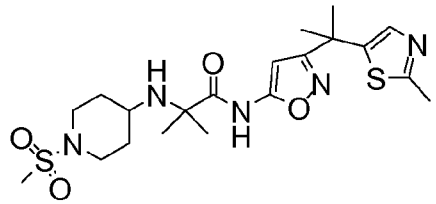
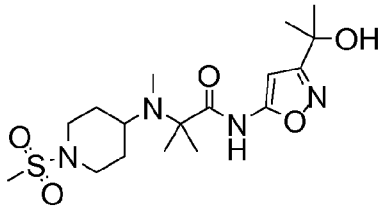
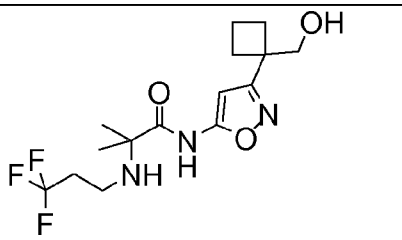
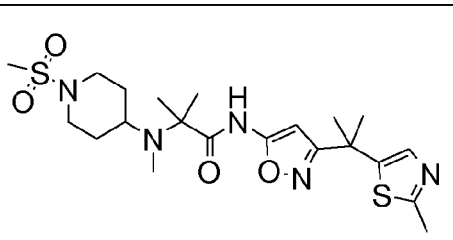
9. A compound according to any of the preceding claims, chosen from

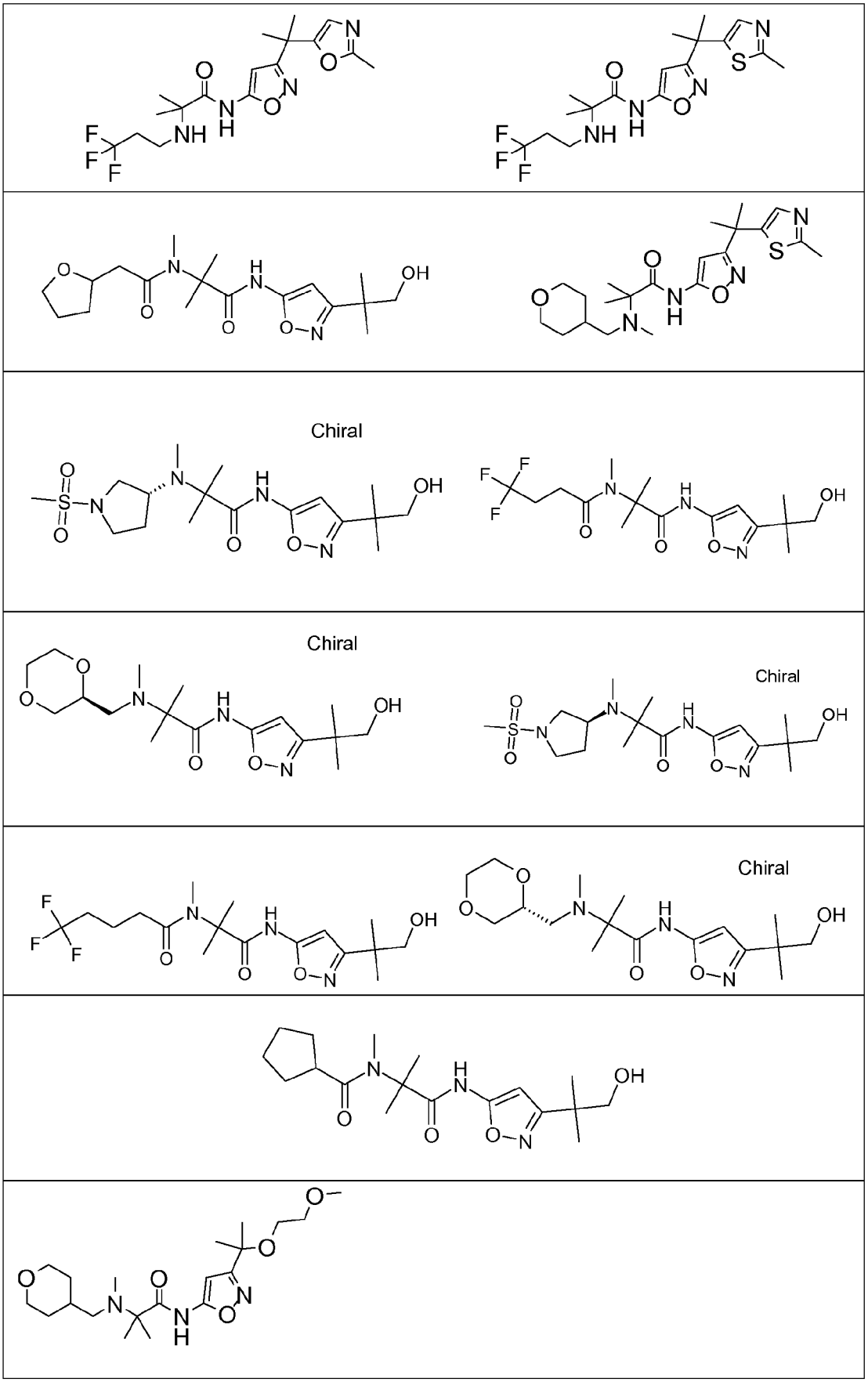
	
	
	
	
	
	
	
	
	







	
	 Chiral
	 Chiral
	
	
	
	
	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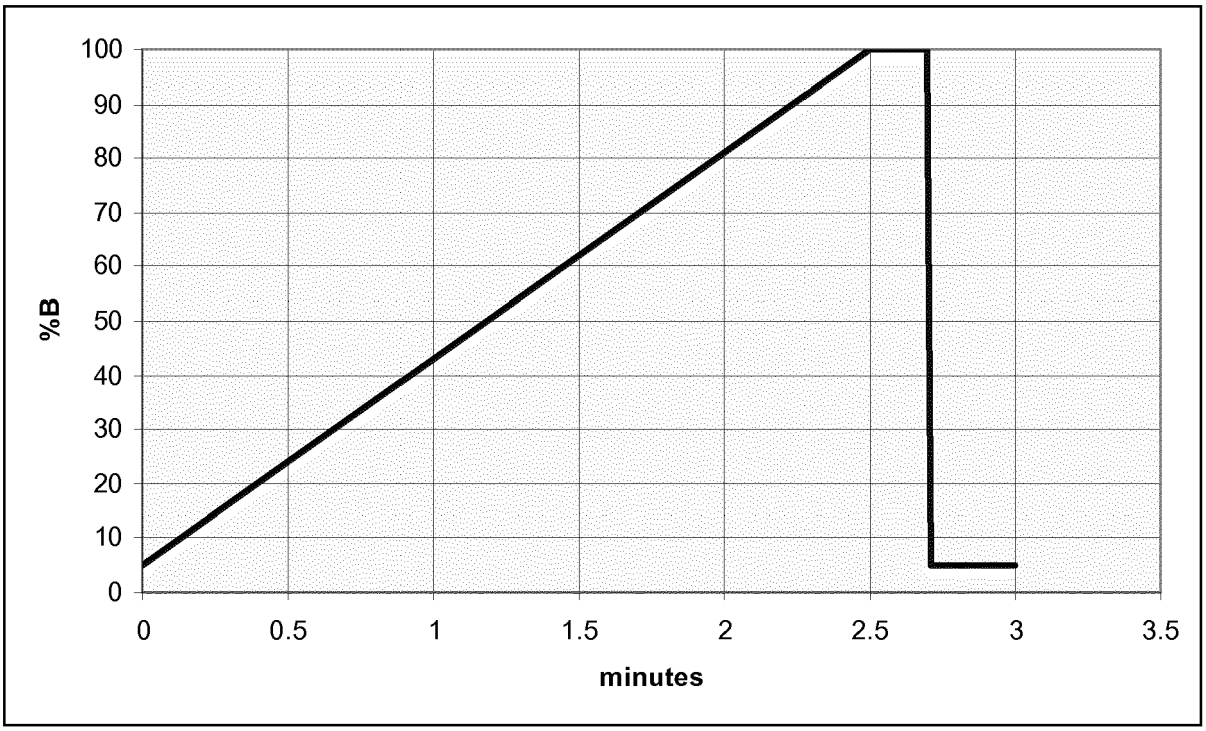
or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of the preceding claims and one or more pharmaceutically acceptable carriers and/or adjuvants.

11. A compound according to any one of claims 1-9 for use in the treatment of a disease or condition chosen from pain, a lung disease, a rheumatic disease, an autoimmune disease, a musculoskeletal disease, an allergic disease, an allergic reaction, a vascular disease, a dermatological disease, a renal disease, a hepatic disease, a gastrointestinal disease, neurodegeneration eye disease, diseases of the ear, nose, and throat, neurological disease blood disease, tumors, endocrine diseases, organ and tissue transplantations and graft-versus-host diseases, severe states of shock, acute pain, visceral pain, spasm of the gastrointestinal tract or uterus, colics, neuropathic pain, inflammatory and nociceptive pain, cancer pain, headache, restenosis, atherosclerosis, reperfusion injury, congestive heart failure, myocardial infarction, thermal injury, multiple organ injury secondary to trauma, necrotizing enterocolitis and syndromes associated with hemodialysis, leukopheresis, and granulocyte transfusion, sarcoidosis, gingivitis and pyrexia.

FIG 1/2

FIG 2/2



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EUROPEAN SEARCH REPORT

Application Number
EP 13 19 6679

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	WO 2008/014199 A2 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; BERRY) 31 January 2008 (2008-01-31) * claims *	1-11	INV. C07D261/14 C07D413/12 C07D413/14 C07D417/06 C07D417/12 C07D417/14 A61K31/42 A61P29/00
A	DIMITRA HADJIPAVLOU-LITINA ET AL.: "Thiazolyl-N-substituted amides: a group of effective anti-inflammatory agents with potential for local anesthetic properties. Synthesis, biological evaluation and a QSAR approach", DRUG DEVELOPMENT RESEARCH, vol. 48, 1999, pages 53-60, XP002599014, * the whole document *	1-11	

TECHNICAL FIELDS SEARCHED (IPC)

C07D
A61K
A61P

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	3 March 2014	Diederen, Jeroen

CATEGORY OF CITED DOCUMENTS

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